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ORIGINAL ARTICLES

OBSERVATIONS ON TYPHOID FEVER IN DETROIT

BY HENRY F. VAUGHAN, EPIDEMIOLOGIST, AND W. FRANK WALKER, SANITARY ENGINEER, DETROIT BOARD OF HEALTH.

THE City of Detroit located on the Detroit River just below Lake St. Clair covers an area of approximately 47 square miles. The United States Census estimate of population for 1915 was 554,717. There is reason to believe, however, that the true population is somewhat in excess of this figure. This is based on the fact that Detroit's growth for the last decenial period was not uniformly distributed; approximately 60 per cent of the increase occurring between the years of 1906 and 1910. This growth parallels the growth of the automobile industry in the city. Because of this irregular increase, the increment based upon the average increase for the last decade and used in making up the United States Census estimate is too low. A census taken by the Water Board, based upon the number of families multiplied by a factor, which has been found by comparison with the United States Census to be fairly reliable gives the population for 1915 as 673,498.

The average width of the river at Detroit is 2,200 feet, with an average depth of 37 feet. The flow of the river as estimated by the United States Engineers is 209,000 cubic feet per second. Gaugings show that approximately 65,000 cubic feet per second flow through the American channel. The river near its head receives the flow of Connors and Fox Creeks which furnish respectively 780 and 150 cubic feet per second at times of flood.

Practically the entire lake traffic passes through the Detroit River, the number of vessels being about 38,000 annually with a net tonnage of 63,000,000 of which about 3,000,000 have Detroit as their destination. Of the 15,000,000 people carried annually by passenger steamers on the Great Lakes, very nearly 10,000,000 are carried by boats operating out of Detroit. Of these 10,000,000 of people nearly 4,000,000 are carried on boats running to cities or resorts at some distance from Detroit either up or down the river. The remaining 6,000,000

are carried by the ferry boats plying between Detroit, Belle Isle and Windsor. Thus Detroit's position is unapproached by any other city on the Great Lakes.

The climate of Detroit is that of the lower Great Lakes Region with a mean

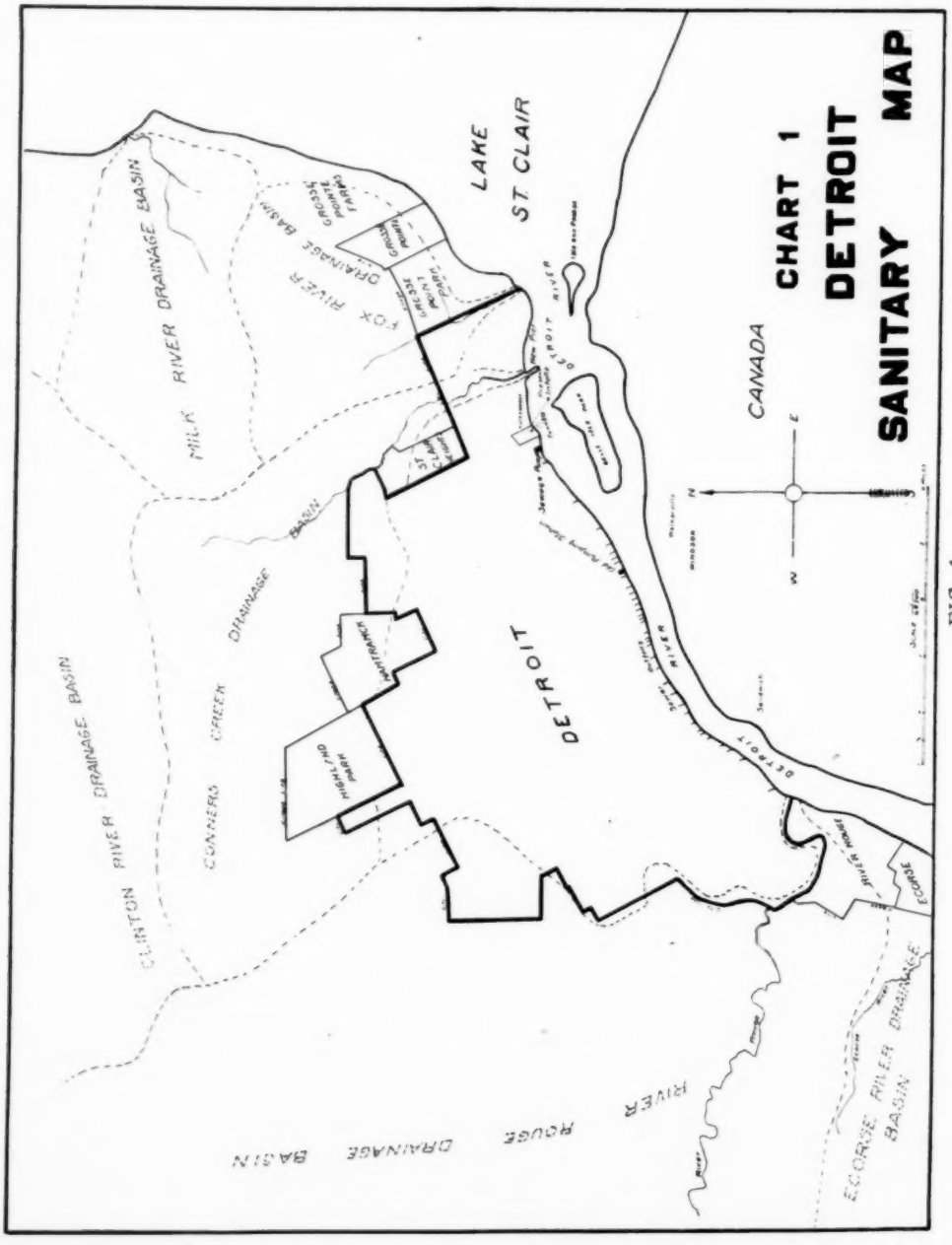

FIG. 1.

annual temperature of 48.2° F. with variations between 24.4° F. for February and 72.1° F. for July, the greatest daily variation being about 34.° F. The mean annual precipitation is given as 32 inches, with a minimum monthly aver-

age of 2.09 inches for January and a maximum monthly average of 3.64 inches for June, the maximum for any one day being 4.57 inches. Wind velocities of 40 miles per hour are not uncommon, the average being about 13 with a maximum of 86. The general direction of the hard winds is from the West or Northwest.

General Health Conditions.

The following table gives, by years, the death rate per 100,000 in Detroit from typhoid fever, scarlet fever and diphtheria:

Year	Typhoid Fever	Scarlet Fever	Diphtheria
1900	28.4	6.3	29.1
1901	20.1	18.0	18.0
1902	23.5	24.2	44.4
1903	20.0	7.1	71.7
1904	17.6	11.3	44.4
1905	20.3	9.1	34.7
1906	20.7	28.1	22.6
1907	25.5	17.7	19.6
1908	19.6	17.7	16.1
1909	20.5	22.3	24.3
1910	23.0	16.2	33.8
1911	16.0	13.2	34.3
1912	17.5	11.8	37 3
1913	29.4	21.3	57.6
1914	13.8	9.5	29.6
1915	13.0	4.5	20.9

It will be seen that in 1914 there was a reduction from 1913 in diphtheria of 48 per cent, typhoid fever 53 per cent and scarlet fever 55 per cent. Likewise 1915 shows a marked reduction over the year immediately preceding. At this time the activities of the Health Department were materially extended and, it is believed, the efficiency greatly increased by the application of new methods. It is of interest to note at this point the relationship existing between the addition of hypochloride of lime to the water, the application of other preventative means for the control of typhoid fever, and the number of deaths by months. Referring to Fig. 16 it appears that the number of deaths from this disease continued to increase after the addition of the disinfectant to the water supply. We might possibly have had a much higher death rate had this form of treatment been omitted but still it seems reasonable to believe that, had the greater part of the typhoid fever at that time been due to the water supply, there would have appeared a reasonable reduction in the numbers of deaths during the months immediately following that date. The reduction of typhoid did not take place until 1914 during which year vigorous efforts were made to prevent contact infection, river water infection, boat infection, milk and food infection, etc. It was at this same time that the reduction became apparent in diphtheria and scarlet fever due to extensive preventive measures. The infant mortality rate was likewise reduced from 136.4 per 1,000 births in 1913 to 120.4 in 1914 and 104.6 in 1915.

A sanitary survey of the city made in 1913 disclosed some six thousand privy vaults within the city limits. The role that these insanitary fixtures are capable of playing in the spread of typhoid fever is well known. This has been

amply demonstrated by the board of medical officers in 1898 and likewise by the reduction, from over 100 deaths per 100,000 in 1910 to less than 30 in 1912, from typhoid fever in Jacksonville, Florida, through the passage and enforce-

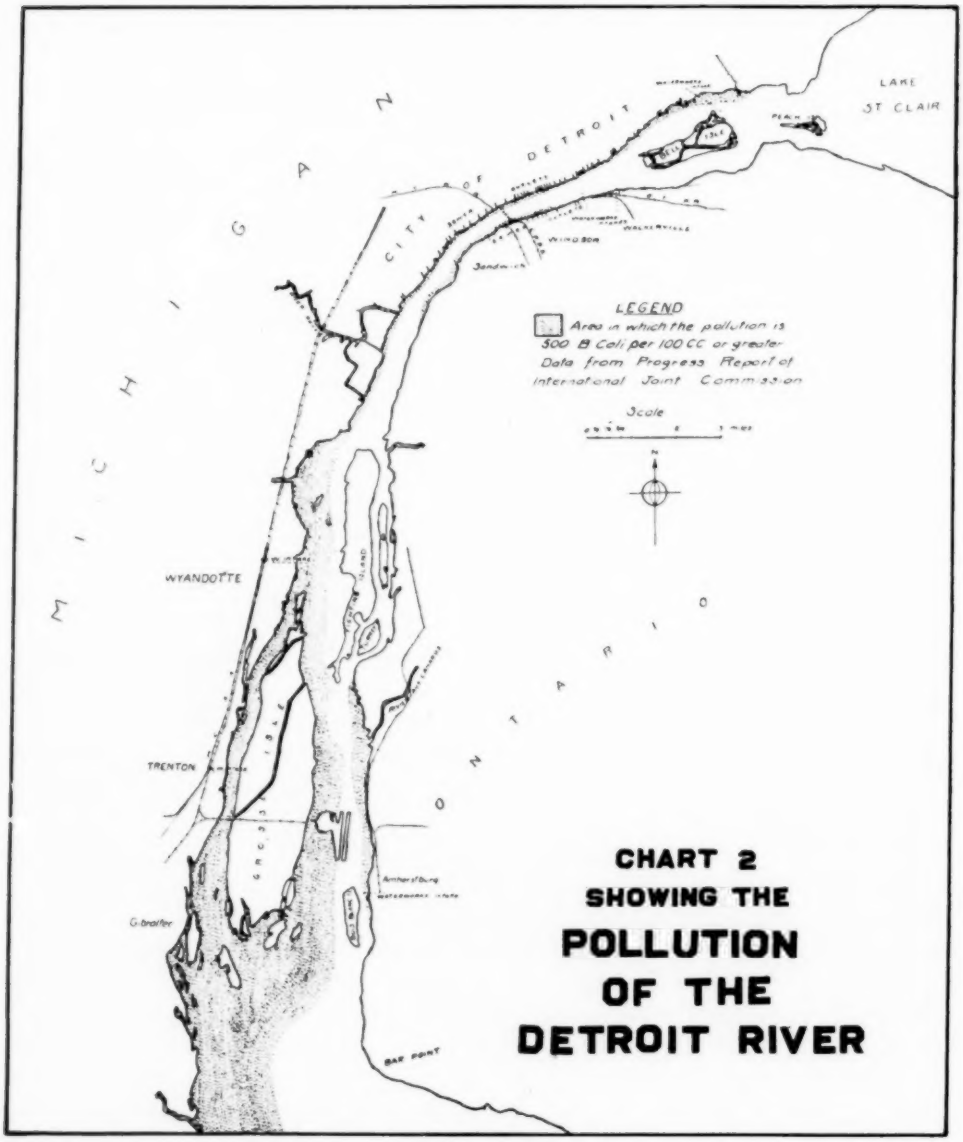

FIG. 2.

ment of a sanitary privy law. In Detroit, privy vaults have been removed and sanitary toilets installed as follows:

1911—1912	492
1912—1913	1,839
1913—1914	1,490
1914—1915	1,340

There are now probably less than 2,000 remaining in the city and these are being replaced as rapidly as time will permit.

During the past summer an extensive antifly campaign was maintained under the jurisdiction of the Board of Health in which some four thousand boys participated. The city was divided into six hundred small districts and each boy was given a map of his district, literature and rules, and was made responsible for his block or group of blocks. This campaign aimed rather at the prevention of flies by destroying the breeding places than at the extermination of great numbers.

Sources of Infection.

In order to obtain uniform and complete data with regard to each case of typhoid fever reported to the Health Department, the usual form of investigation card has been adopted. The following items are included: name, address, sex, color, nativity, occupation, visitors, visits made; date of first symptom, date of taking bed, date of doctor's first call, doctor, date reported; schools, number in family, adults, children, servants; previous typhoid histories and dates, personal contact, at home, at business, in cars; sanitation; milk; drinking water, present, 2 to 3 weeks before sick; ice; fresh vegetables, oysters and food, dealer's name; hospital; tests and results; termination; length of time in city; previous residence; boat and other excursions during the past month, date, locality, and drinking water; associates on excursions, their histories; bathing places and dates; visits to hospitals, etc.

The results have been found far more trustworthy when obtained by assigning one especially instructed investigator to the typhoid work than by relying upon the district nurse to obtain the information in the course of her other duties. This same nurse likewise instructs the members of the household regarding the care of the patient and makes the necessary demonstrations to assure the carrying out of all disinfections. Literature, amply illustrated, is provided describing the cause and methods of prevention.

Up until the spring of 1914 typhoid fever was not sufficiently reported in Detroit to justify any extensive epidemiological studies. At that time through the medium of the leading newspapers which printed appropriate charts and diagrams on their first pages and by court action, suitable publicity was given to the subject with the result that during the eighteen month period, July 1, 1914, to January 1, 1916, there have been 884 cases brought to the attention of the Health Department. The majority of these were reported by the attending physicians and a few were picked up by the investigating nurse. The accompanying table (Fig 3) gives the number of cases and deaths by months.

Dr. Wm. H. Price, Health Officer, in the January, 1916, bulletin states: "During 1915, 50 per cent of deaths reported as typhoid fever had not previously been reported as cases. Failure of these reports cripples the Board of Health both in taking of necessary measures for sanitary control and in providing accurate information for formulating a city policy relative to water supply and sewage disposal. The Board of Health has attempted through publicity, personal interviews and prosecutions to correct this failure of reports both regarding typhoid fever and other reportable diseases."

TYPHOID CASES AND DEATHS BY MONTHS.
DETROIT, MICH.

MONTHS	INSTANCES	CASES RECOVERING	DEATHS	RATIO of INSTANCES to DEATHS	CASES REPORTED	DEATHS REPORTED as CASES.
1914 JULY.	69	58	11	6.25	59	6
AUG.	99	90	9	11.00	83	2
SEPT.	103	93	10	10.30	98	5
OCT	73	69	4	18.30	56	1
NOV	53	46	7	7.50	3.9	4
DEC	30	22	8	3.70	25	5
TOTAL for 6 months	427	378	49	8.72	360	23
JAN	19	18	1	19.00	17	1
FEB	18	14	4	4.50	16	3
MAR	26	22	4	6.50	22	2
APR	15	12	3	5.00	11	2
MAY	23	19	4	5.70	19	1
JUNE	20	19	1	20.00	19	1
JULY	47	36	11	4.26	40	5
AUG	73	68	5	14.60	63	1
SEPT.	91	81	10	9.10	86	7
OCT	52	46	6	8.70	51	6
NOV	40	28	12	3.33	34	6
DEC	33	22	11	3.00	30	8
TOTAL for 12 months	457	385	72	6.35	408	43
TOTAL for 18 months	884	763	121	7.30	768	66

FIG. 3.

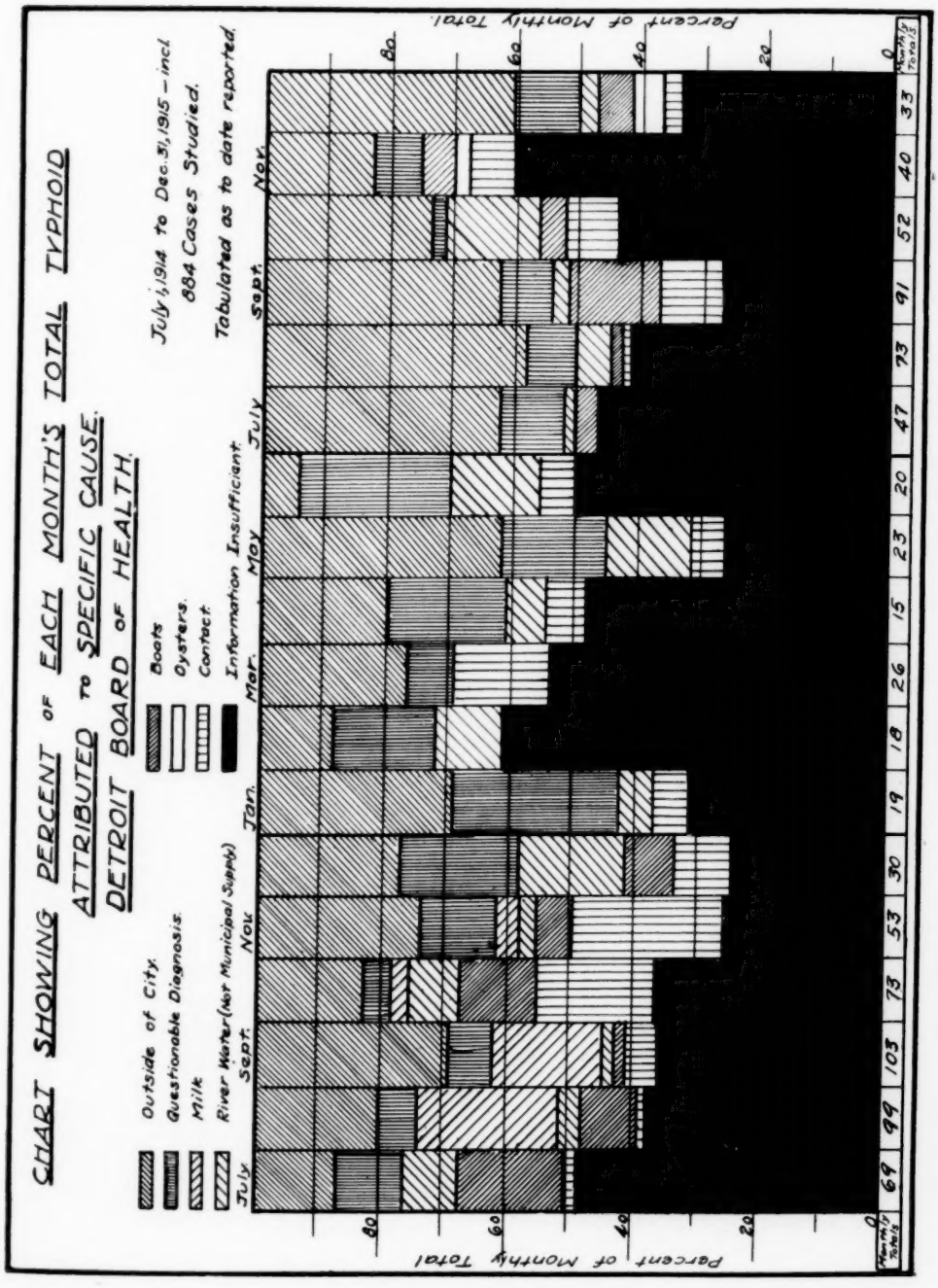
CHART SHOWING PERCENT OF EACH MONTH'S TOTAL TYPHOID ATTRIBUTED TO SPECIFIC CAUSE. DETROIT BOARD OF HEALTH.
July 1, 1914 to Dec. 31, 1915 — incl.
884 Cases Studied.
Tabulated as to date reported.
Outside of City.
Questionable Diagnosis.
Milk
River Water (Not Municipal Supply)
Boats
Oysters.
Contact
Information Insufficient.
July Sept. Nov. Jan. Mar. May July Sept. Nov.
Percent of Monthly Total
Monthly Totals
69 99 103 73 53 30 19 18 26 15 23 20 47 73 91 52 40 33

FIG. 4.

It has been our aim to make a detailed analysis of the history of each case and from such a study to draw a conclusion as to the probable source of infection. In 337 cases, or 38 per cent of the instances, we were unable to ascribe any particular source. As in the compilation of mortality statistics it is a difficult problem to select a single cause of death from two or more causes simul-

taneously reported by the physician, it is likewise not a simple matter to assign with certainty a specific source of typhoid fever infection in every instance. Consequently this has been done only in those cases in which the evidence is most conclusive. The accompanying chart (Fig. 4) shows the per cent of each month's total typhoid attributed to each specific source.

Outside.—This refers especially to nonresidents who come to Detroit sick, or who are taken sick at the proper time after their arrival. Lumsden and Anderson report: "As the incubation period of typhoid fever is by no means sharply defined, it is not possible to determine exactly, from a consideration of the element of time alone, on what day or within what period of even ten days the infection has been contracted in a particular case; but, since in the vast majority of cases, certainly, the infection is contracted at some time within a period of thirty days prior to onset of illness and in a considerable majority probably at some time within a period of ten days ending eight days before onset of illness, the place of infection may be determined with a reasonable degree of accuracy in most instances."

This classification would include a case from Royal Oak brought to a Detroit hospital; a person returning sick from a month's outing at some summer resort, and the like. Fig. 4 shows this item to be rather high at those periods when people are returning from their summer homes and their outing trips. The percentage continued rather high throughout the entire eighteen months, due to the number of nonresidents who are brought to Detroit hospitals.

Questionable Diagnosis.—This includes only those cases in which the evidence was most convincing that the patient did not have typhoid fever. It would be an endless task to relate the evidence on which each questionable diagnosis is based since this would require the submitting of numerous letters to physicians, their replies, and the direct evidence of nurses and attendants.

Milk.—Unquestionable evidence of milk infection was found in A's milk during the month of August, 1914, when some 35 cases of typhoid appeared on his route within the city, and many more scattered throughout the villages immediately east of the city line. His milk supply was immediately cut off from the city and the spread of the infection ceased. There was an active case of typhoid on A's farm. Two or three instances of milk infection appeared later on the west side of the city. It is believed that the compulsory pasteurization of all milk, which action took effect in May, 1915, has practically eliminated all possible source of milk infection.

River.—Most of the commercial enterprises situated along the river front have a dual water system, obtaining their supply both from the city mains, this water having undergone the chlorination process of treatment, and directly from the river. Their river intakes are, scarcely without exception, located immediately below some of the large city sewers, consequently the water is highly charged with the colon bacillus, unoxidized organic matter and probably with some specific pathogenic organisms.

The results of a survey made among these factories appear elsewhere in this report. In not a few instances wholesale outbreaks of dysentery among the employees, and many cases of typhoid have been traced to raw river water.

This source of infection was unusually severe during December, 1914, when it was found at one of the manufacturing plants that the employees were provided with river water in all the wash rooms and that the only available supply in the boiler room was from this source.

Boats.—This includes primarily cases from the Marine Hospital, sailors who have been taken sick on boats and removed therefrom at Detroit. There is, of course, some question as to whether this ought not be placed under the heading "Outside" but it has been thought advisable to attempt to subdivide further and charge the boats with their fair portion. Some cases are charged against this class in instances where two or three friends have taken boat trips, afterward developing typhoid, and we have positive knowledge that the boat in question carried a polluted water supply.

During the month of September, 1915, there were reported 14 cases charged against the boats. Twelve of these 14 cases were members of a naval reserve squad which cruised to Erie, Pa., and Buffalo, N. Y. Numerous cases developed in other cities among the members of the crew. The epidemic was investigated by the Public Health Service and the efforts of the Detroit Health Department were confined to the prevention of secondary cases.

Oysters.—During the latter part of 1915 there were reported three cases in which the evidence proved most conclusively that oysters had been the cause of the infection.

Contact.—This item includes unquestionable cases of direct contact such as infection received by brothers and sisters from other members of the immediate family; landladies who have taken care of boarders sick with the disease, etc. It does not include any chance contact by indirect means, as for example, fly contact. Contact appeared but slightly during the summer but found a very prominent place in the autumnal typhoid.

Contact infection is the most common mode in the distribution of typhoid, the medical board of officers in 1898 having placed the percentage at 62.8, while Drigalski, some nine years later, gave for Germany 64.7 per cent. The board further divides contact as follows: direct, 35.01; indirect, 27.79 per cent. It is undoubtedly true that had our information in many instances been more complete, the percentage of contact cases, including indirect, would have been much higher.

Information Insufficient.—This class includes those cases in which we were unable to procure sufficient information to specify any direct source of the disease. However, it is highly possible that had we been able to obtain more history regarding the case, it might have been placed under one of the other seven classifications.

Frequently the wrong address is given when a case is reported, or the "sick" person has moved. Often it was found impossible to converse with the person interviewed or possibly the latter didn't care to understand. In case a death has not previously been reported as a case, it is difficult to obtain sufficient information from the friends or relatives of the deceased.

Geographical Distribution.

Figs. 5 to 11, inclusive, classified as to source of infection, show the distribution of typhoid instances throughout the city. Fig. 5 shows the cases in

which the infection was obtained outside of the city. As would be expected they appear scattered about the more well-to-do sections of the city. A comparative study of the maps showing the distribution of infant births, tuberculosis and

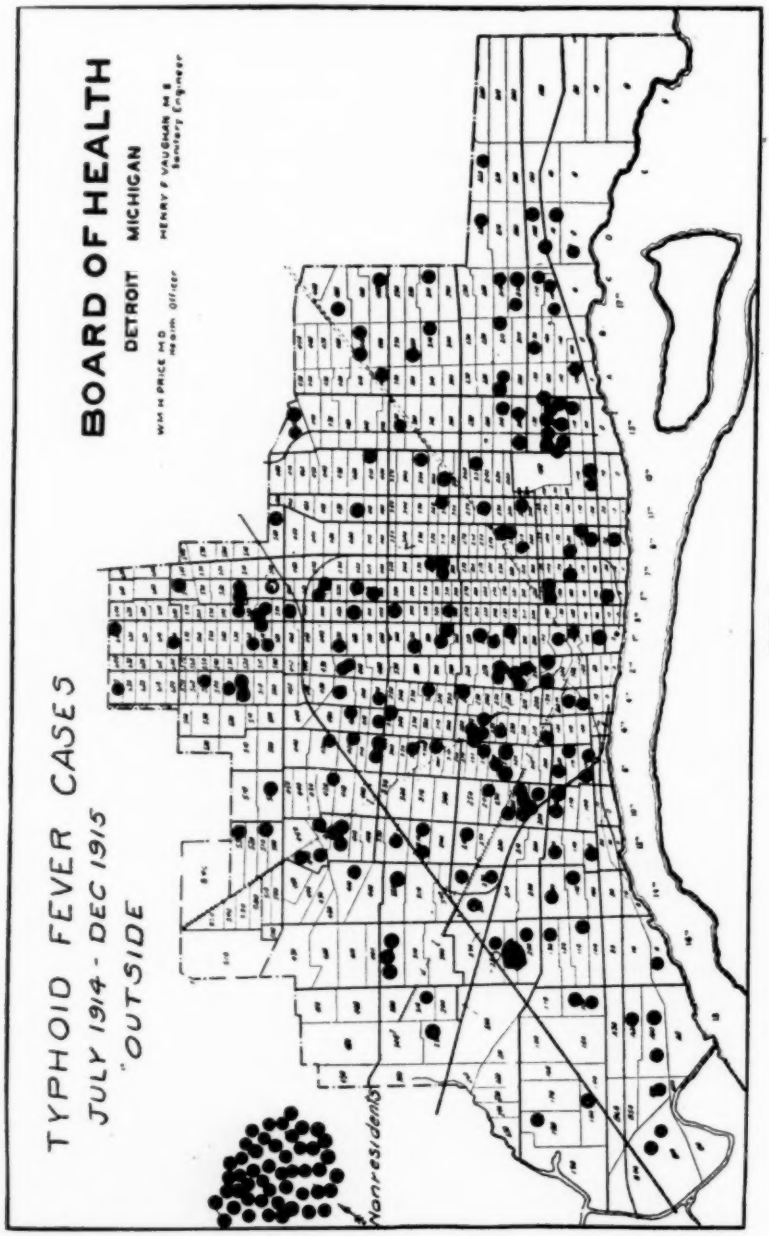

FIG. 5.

pneumonia, shows a decided dissimilarity. Typhoid fever has not been as marked in those districts in which crowded conditions exist—the dirtier districts in which the people are accustomed to remain at home and do comparatively little traveling. These are the districts in which the density of population is the greatest.

Fig. 11 is the one exception to this. During the warm months it appears that a considerable portion of the cases existed in the third, fifth, seventh, ninth and eleventh wards. These were cases which gave no history of having been out-

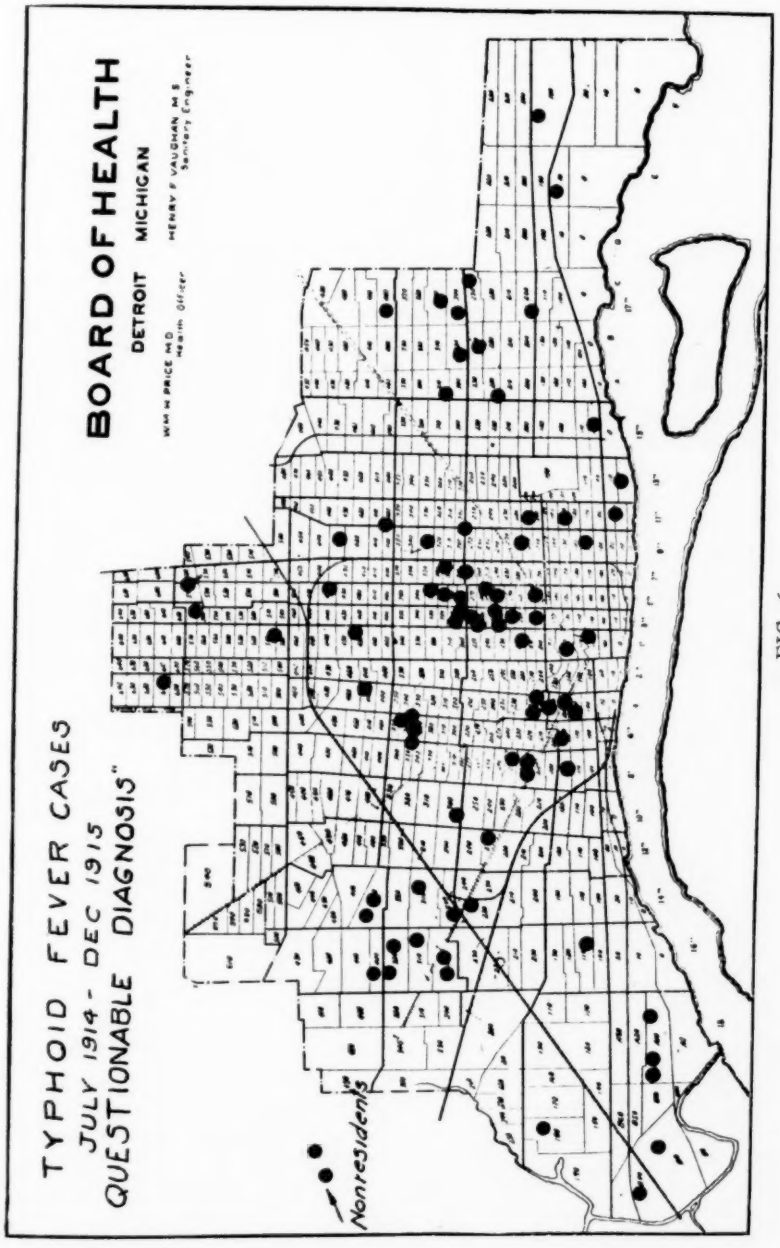

FIG. 6.

side of the city, the information obtained being altogether insufficient to assign any definite source of infection. The prevalence of flies, manure, filthy alleys, uncovered garbage, crock hoppers, and open privies may have played some part in the spread of this infection.

Fig. 7 is of considerable interest in showing the needless havoc that may be wrought by a single milk producer. This shows only a small portion of the cases which resulted from the infection of this milk supply, as many other cases lived in the villages immediately adjoining the city to the east.

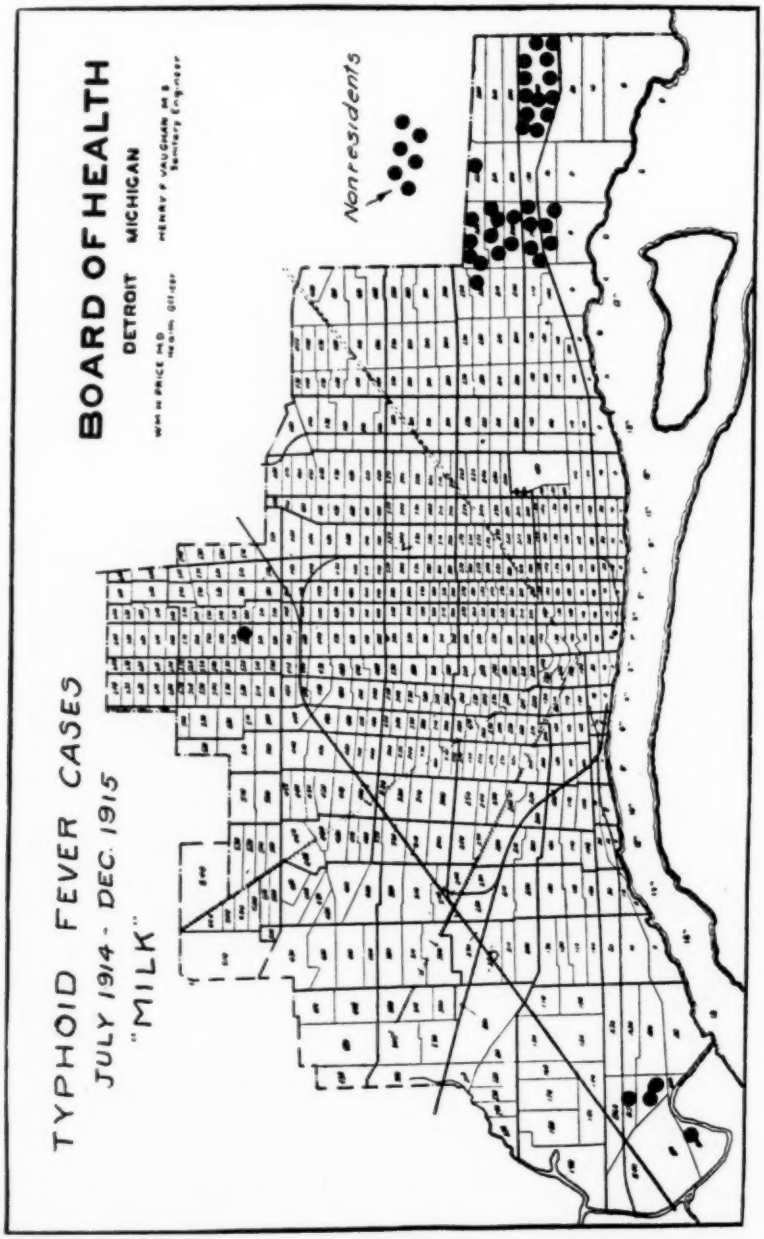

FIG. 7.

SEX.

The accompanying chart (Fig. 12) shows the percentage of cases in males occurring during the first twelve months of the study. As might be expected

the percentage among males is, in general, higher than that among females, probably due to the practice of the former of eating at serve-selfs, restaurants or other eating houses away from home. However, during the winter months the

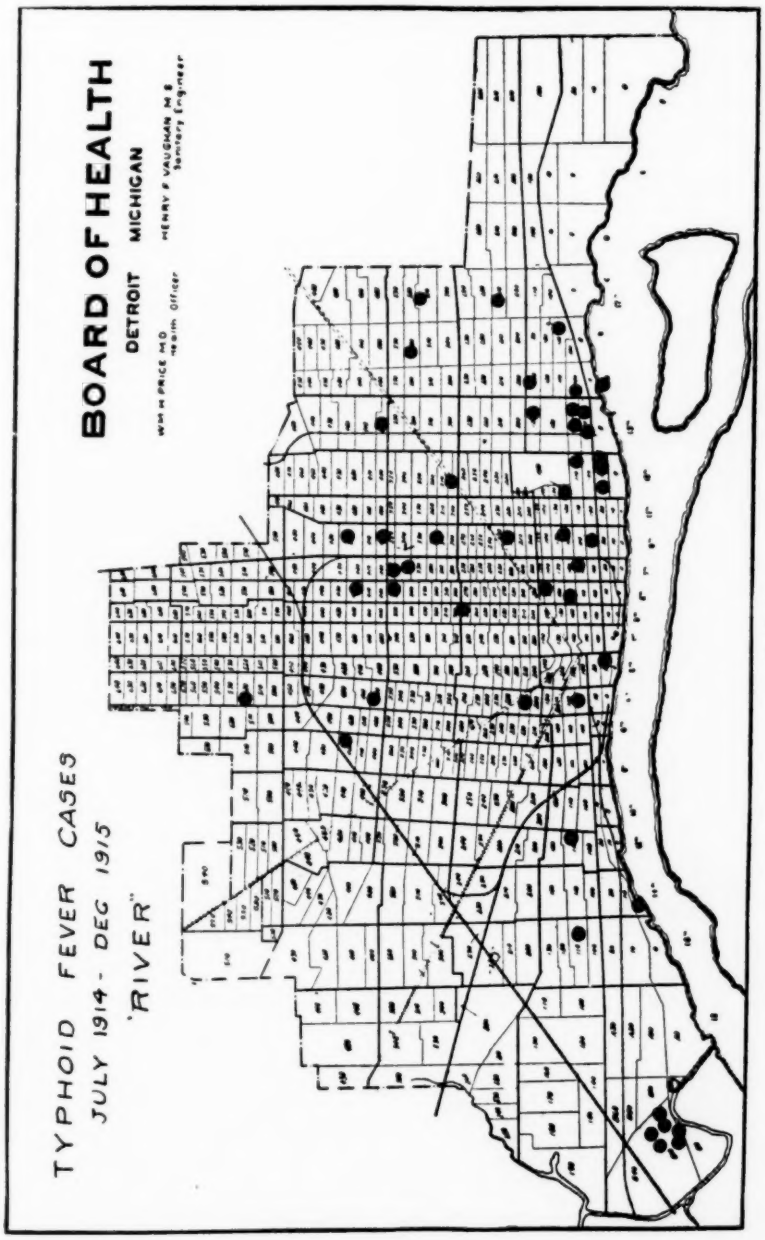

FIG. 8.

number of cases is more evenly divided between the males and females. Possibly some other factor played an important part at this time, some food or drink used pretty generally by both the sexes.

AGE.

Fig. 13 shows the distribution of cases among persons in the different age groups, according to months of onset of illness and sources of infection. Fig.

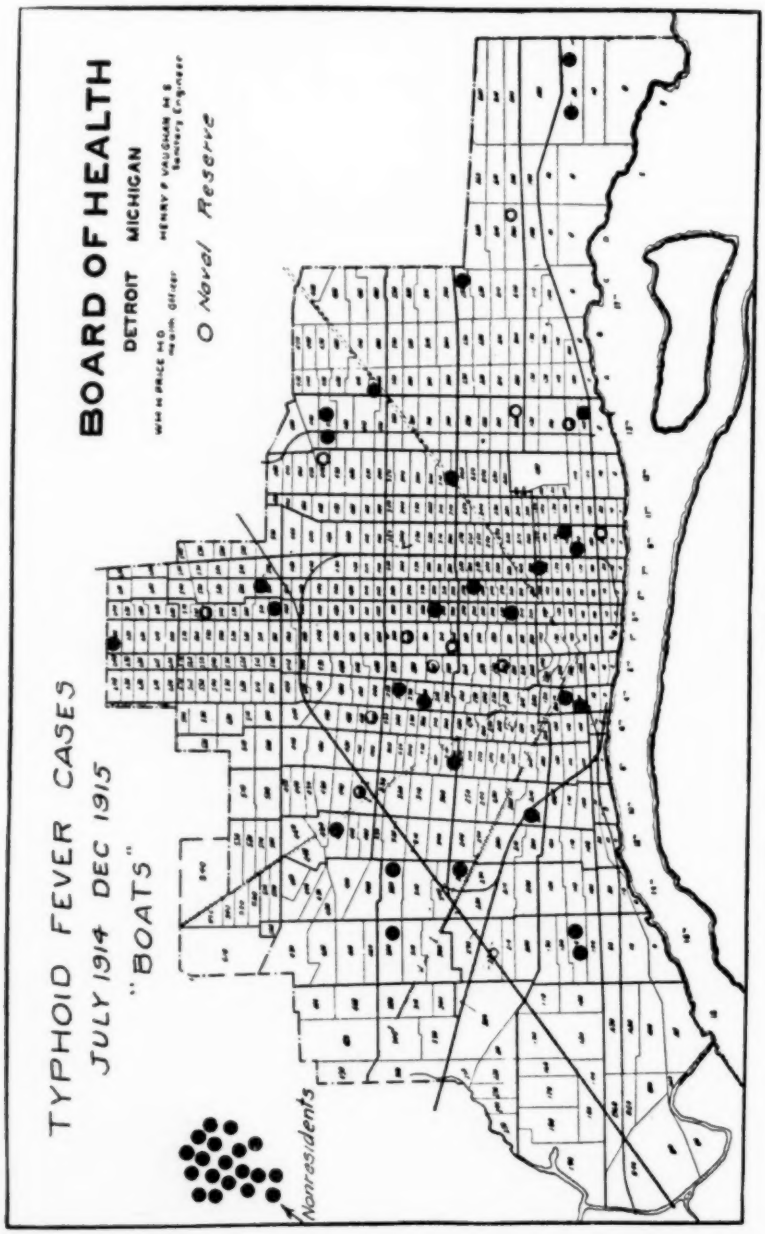

FIG. 9.

14 shows the percentage of cases, by months, furnished by persons in different decades of life.

Of the cases occurring in January, children under ten years of age appear to have furnished 28.5 per cent of the disease. In winter outbreaks caused by

infection conveyed by a public water supply, the percentage of instances among children under ten years of age, who with adults would be equally exposed, has been found to be between 15 and 20. The high percentage would look rather

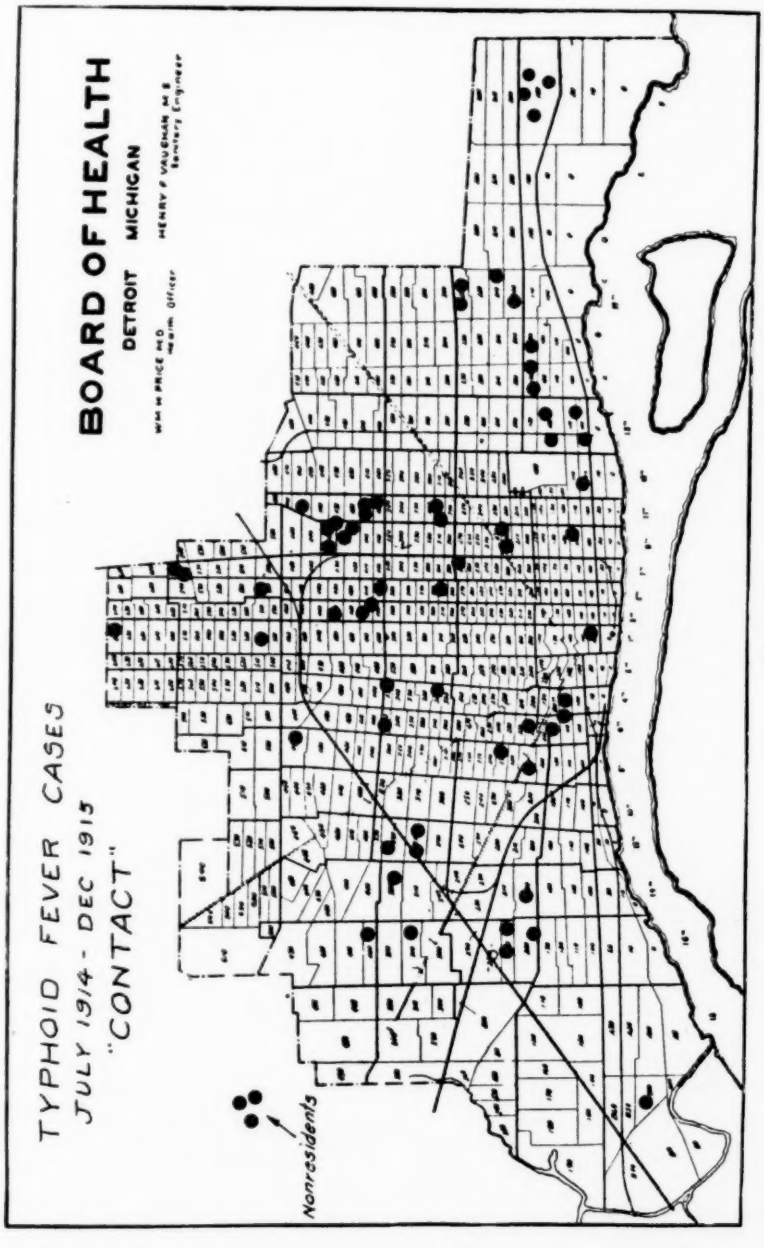

FIG. 10.

suspicious but on further analysis of Fig. 13 we find that of the six cases constituting 28.5 per cent of the January total, 5, or 83 per cent, have been assigned some definite classification. Four of these cases were error in diagnosis which, eliminated, would reduce the percentage at this age group to 9.5 which is far

below the suspicious mark. The percentage of cases among children seems to be rather consistent throughout the year. There is no marked increase during the warm months at a time when they are more subject to general digestive

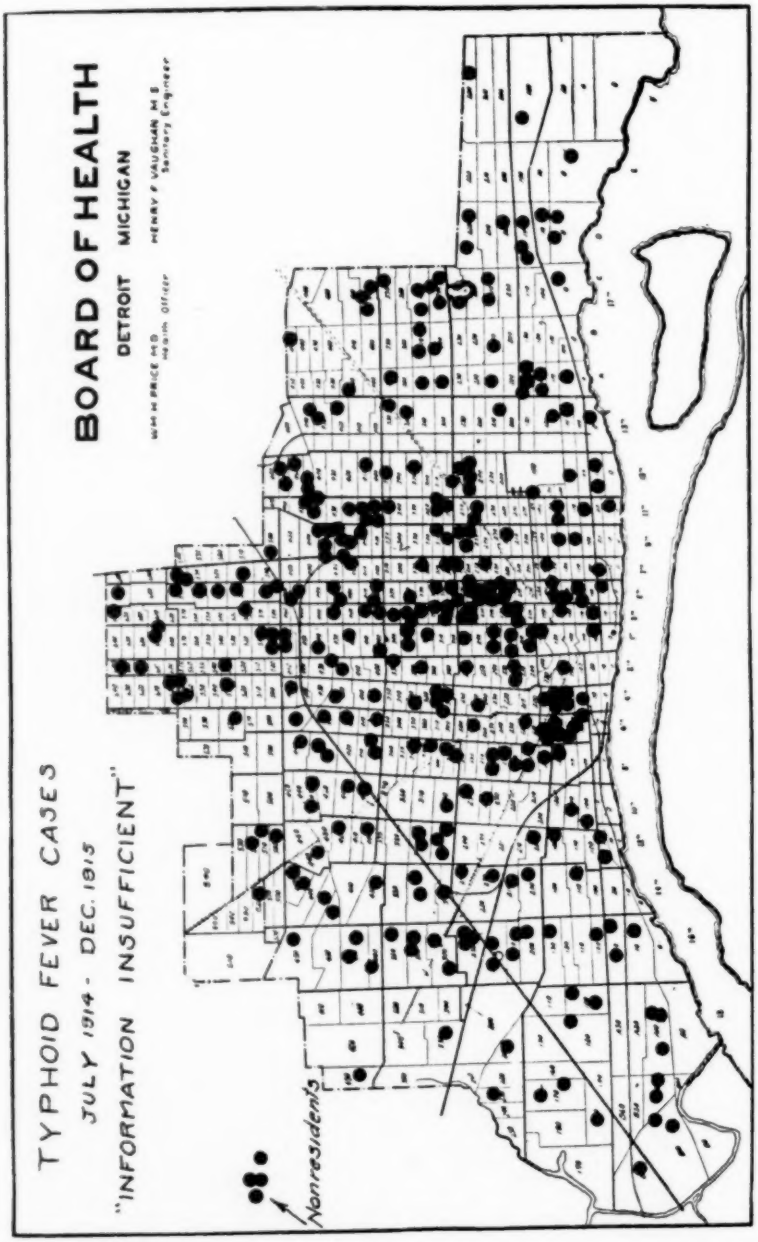

FIG. 11.

disturbances than are adults. Had children been subject to the same infection as adults throughout the year it seems that we might have expected a higher percentage among children during the summer. Evidently there have been some factors especially active during the summer months which have affected

NUMBER OF CASES OF TYPHOID FEVER BY SEX

Month	June	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	Un-known
Male	15	41	79	46	39	21	14	11	8	8	10	12	4	23
Female	8	27	48	31	24	13	3	10	16	8	5	12	5	7
Total	23	68	127	77	63	34	17	21	24	16	15	24	9	30
% Male	65	60	62	60	62	62	82	52	33	50	67	50	44	77
Month	June	July	Aug	Sep.	Oct.	Nov	Dec	Jan.	Feb.	Mar.	Apr.	May	June	Un-known

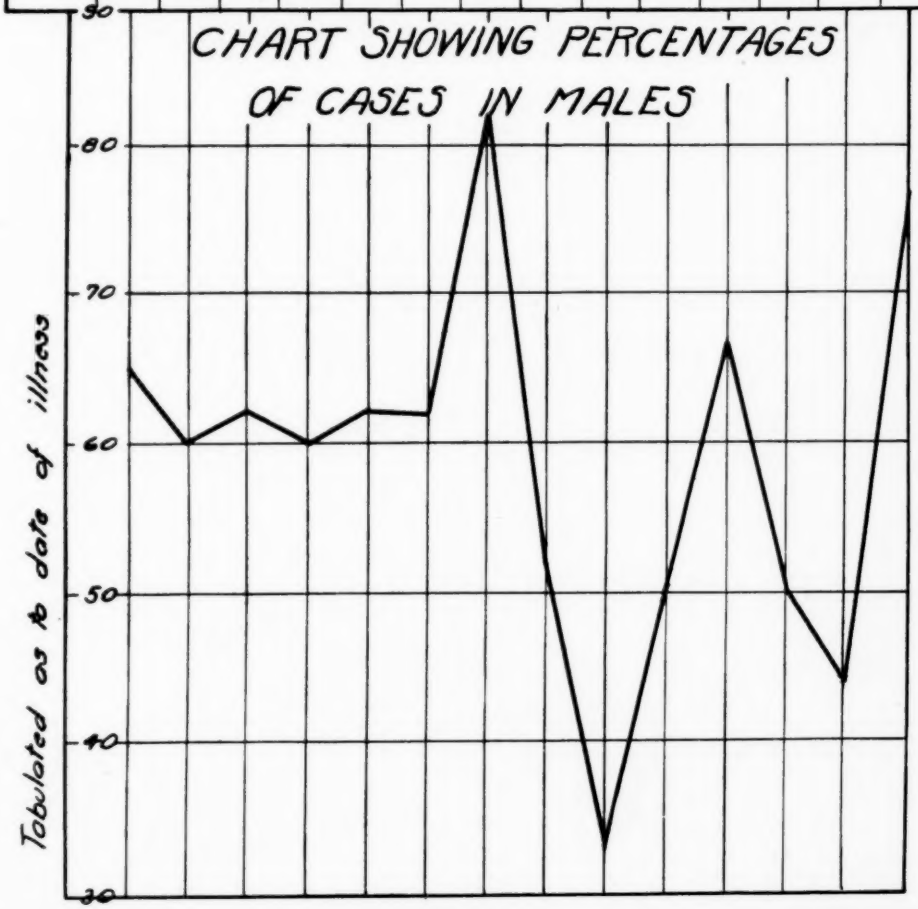

FIG. 12.

only adults. There seem to have been comparatively few people between the ages of 20 and 30 who contracted the disease during March and April. During the remainder of the period this percentage did not change materially.

TYPHOID FEVER STUDIES

BY AGE GROUPS AND SOURCES OF INFECTION.

Key to Source. 1. Outside. 2. Insufficient Information 3. Other Sources 4. Total

Cases Studied = 808

June-1914 thru Dec.-1915.

Age Groups	NUMBER OF CASES TAKEN SICK IN																								Age Groups
	June.				July.				Aug.				Sept.				Oct.				Nov.				Dec.				
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
0-9	-	2	2	4	1	3	2	6	1	7	11	19	2	3	4	9	-	5	3	8	-	-	1	1	1	-	1	2	0-9
10-19	-	5	-	5	2	9	11	22	10	11	14	35	2	5	3	10	1	6	5	12	3	2	6	11	-	1	-	1	10-19
20-29	2	2	3	7	6	8	7	21	7	13	13	33	10	10	11	31	7	7	10	24	2	2	6	10	1	4	3	8	20-29
30-39	1	1	-	2	1	9	2	12	5	6	10	21	4	5	2	11	1	-	6	7	4	-	4	8	1	-	3	4	30-39
40-49	-	1	-	1	-	1	1	2	3	3	1	7	1	4	3	8	-	3	3	6	-	-	2	2	-	1	-	1	40-49
50-59	-	-	-	-	-	1	-	1	2	1	1	4	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	-	50-59
60-	-	-	-	-	-	2	-	2	1	-	-	1	1	1	-	2	-	-	1	1	-	-	-	-	-	-	1	1	60-

	Jan.				Feb.				Mar.				Apr.				May.				June.				July.				
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
0-9	1	1	4	6	-	1	2	3	-	1	-	1	1	1	1	3	2	1	-	3	-	1	2	3	1	3	2	6	0-9
10-19	1	-	-	1	-	4	1	5	2	3	1	6	-	2	-	2	1	1	1	3	1	1	1	3	7	10	1	18	10-19
20-29	2	6	1	9	1	7	1	9	-	1	1	2	1	-	-	1	4	5	3	12	4	4	5	13	4	6	3	13	20-29
30-39	-	2	2	4	1	1	1	3	-	1	1	2	1	2	-	3	-	1	1	2	4	3	1	8	2	4	1	7	30-39
40-49	1	-	-	1	-	2	-	2	1	-	2	3	-	1	2	3	-	2	-	2	2	2	1	5	-	2	1	3	40-49
50-59	-	-	-	-	-	2	-	2	1	-	1	2	-	1	1	2	-	-	1	1	-	1	-	1	-	1	-	1	50-59
60-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	1	1	-	-	-	-	-	-	-	-	60-

	Aug.				Sept.				Oct.				Nov.				Dec.				Totals.				
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	
0-9	4	2	1	7	3	3	3	9	3	-	2	5	3	1	-	4	1	1	1	3	24	36	42	102	0-9
10-19	9	6	4	19	6	2	6	14	3	4	2	9	-	3	1	4	-	2	1	3	48	77	58	183	10-19
20-29	10	10	12	32	8	6	5	19	5	10	5	20	3	7	4	14	4	2	2	8	81	110	95	286	20-29
30-39	3	2	1	6	2	5	1	8	4	3	2	9	-	3	1	4	1	2	1	4	35	40	50	125	30-39
40-49	5	2	-	7	2	3	3	8	3	-	4	7	1	2	1	4	1	2	-	3	20	31	24	75	40-49
50-59	-	1	-	1	1	-	-	1	-	3	-	3	1	1	1	3	-	-	-	-	5	12	6	23	50-59
60-	-	3	1	4	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	2	7	5	14	60-
																					215	313	280	808	

FIG. 13.

PREVALENCE.

Fig. 15 illustrates the prevalence of typhoid fever divided into the seven classifications which have already been described. The cases are tabulated as

to date of illness, that is, the date on which the patient went to bed, which date can usually be recalled. The time of infection, in most cases, will precede the date of illness from about ten to twenty days.

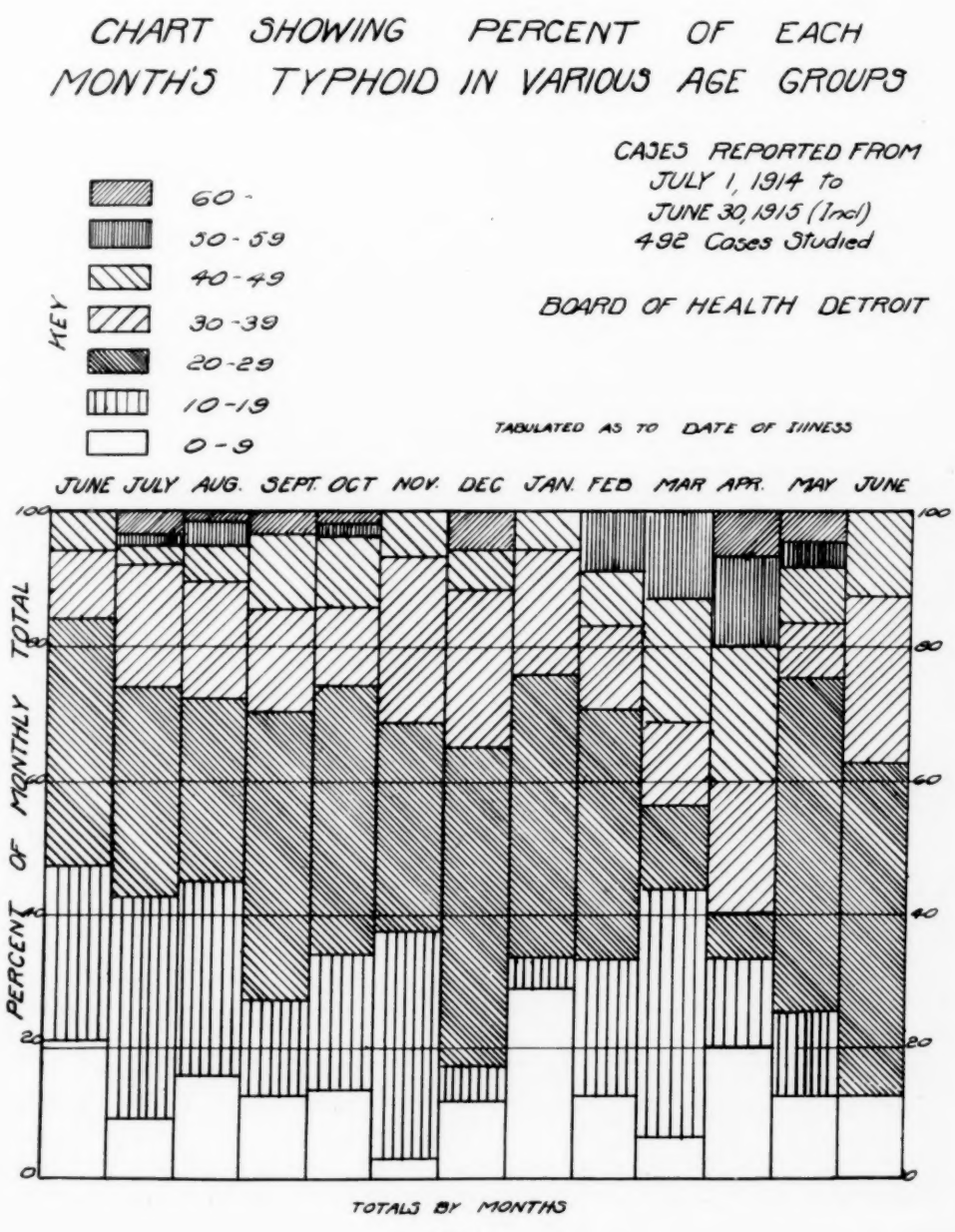

FIG. 14.

Tabulation has been made of typhoid cases by race, occupation, sanitation of homes, etc. Because of the general method which we have adopted in classifying the sources of infection, it seems superfluous to submit these tables at this

PREVALENCE OF TYPHOID FEVER

Sheet #1

Key to Source
1 Outside
2 Questionable Diagnosis
3 Milk
4 River
5 Boats
6 Contact
7 Information Insufficient

1914 - 1915

Month	Source	Day of Month / Date of Illness																												
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1914 June	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	1	-	-	
	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	
	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	4	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	
	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
	7	-	1	1	1	-	-	-	-	-	-	-	-	-	1	-	-	-	-	1	1	2	-	1	-	-	-	1	1	1	-
July	1	1	-	1	-	-	-	-	-	-	1	-	-	-	-	1	3	-	1	-	1	-	-	-	1	-	-	-	-	-	
	2	-	-	-	-	1	-	1	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
	4	1	1	-	-	-	-	-	-	-	-	-	-	-	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	1	-	-	-	2	1	1	-	-	-	1	-	1	-	2	-	1	1	-	-	1	-	-	-	-	-	-	-	1	-	-
	6	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	7	6	3	1	2	-	-	-	1	-	1	1	1	2	1	-	-	-	1	-	1	1	1	1	-	1	3	-	2	-	-	1
Aug	1	2	-	1	2	3	-	3	1	1	-	-	-	3	1	2	-	2	-	3	-	1	1	1	-	-	1	1	1	2	1	1
	2	-	-	-	-	-	-	-	-	1	-	1	-	1	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
	3	3	-	-	-	1	-	-	-	-	-	2	-	1	2	3	1	2	2	1	1	2	5	3	1	1	-	1	1	1	-	-
	4	1	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	1	-	-	-	-	-	1	
	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-
	7	1	-	1	-	4	2	4	-	2	-	-	2	1	3	1	1	1	3	-	2	1	3	-	1	1	-	2	1	3	1	-
Sept	1	2	-	-	-	1	2	1	-	-	2	2	-	3	1	-	1	1	-	-	1	1	-	-	-	2	2	-	-	-	-	-
	2	1	1	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-
	3	2	-	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	-	-	-	-	1	-	-	-
	5	-	-	-	1	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-
	6	-	-	-	-	-	-	-	-	1	-	-	-	-	2	1	-	-	1	-	2	-	-	-	-	-	-	1	-	1	1	-
	7	1	-	1	1	3	2	2	2	1	-	2	1	1	3	-	-	-	-	1	2	-	-	-	1	2	1	2	-	-	-	-
Oct	1	1	-	-	2	-	-	-	-	-	3	1	-	-	-	-	-	-	-	-	1	-	-	-	-	1	-	-	-	-	-	1
	2	1	2	-	-	-	1	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-
	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	1
	4	2	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-
	5	-	1	-	-	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6	1	-	2	1	-	-	1	-	-	1	-	1	-	-	-	-	-	-	1	-	-	-	-	2	1	-	-	-	1	2
	7	3	-	1	1	-	-	2	-	-	1	1	-	-	2	-	-	-	-	-	-	1	-	-	-	1	4	-	1	-	-	1

FIG. 15 A.

time. Moreover, very little is known regarding the actual distribution of population by race and occupation as Detroit's growth since the last enumeration by the Census Bureau has been phenomenal. The location of the industry, rather than the nature of the industry, has entered into the problem.

Water Supply.

Detroit's water supply has at all times been drawn from the Detroit River, not far from the American shore, the first pumping station being located at the

foot of Orleans Street and drawing water 150 feet from shore. This was used until 1877, when the present plant was put into operation, which drew water through three pipes, two of these were 1,500 feet long and 6 feet in diameter,

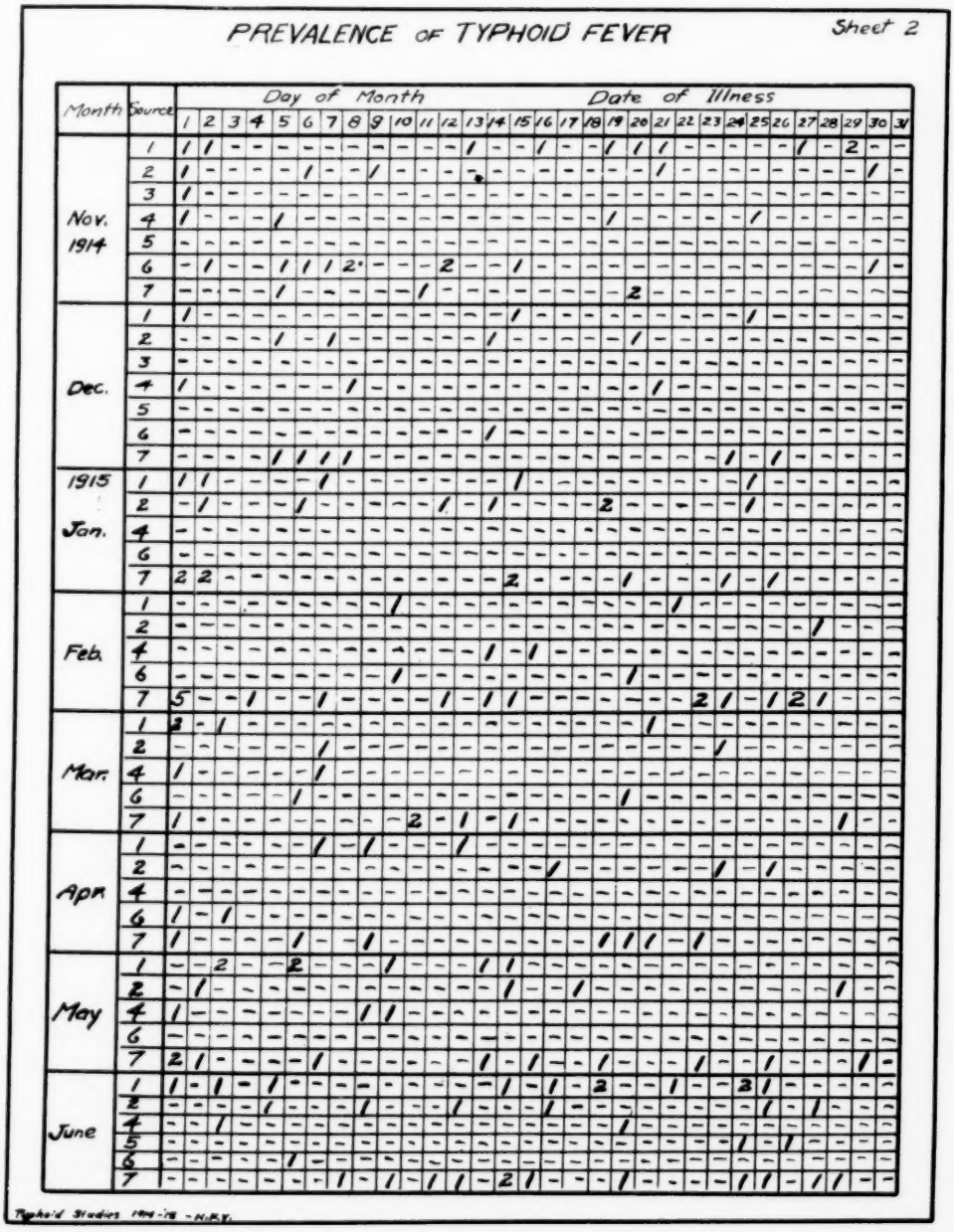

FIG. 15 B.

the other, 1,000 feet long and 5 feet in diameter. These pipes discharged into a settling basin of 30,000,000 gallons capacity, from which the pumps drew their supply.

The question of location of the intake, in order to eliminate the dangers of immediate shore pollution, has always been given serious consideration. The present intake was located near the northwestern extremity of Belle Isle, after a careful and extensive study of the currents in the lower end of Lake St.

PREVALENCE OF TYPHOID FEVER — Sheet 3

Month	Source	Day of Month / Date of Illness																													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
1915 July	1	1	-	-	1	1	-	1	-	-	-	-	-	1	-	-	1	-	1	1	-	-	-	1	-	-	3	2	-	-	1	1
	2	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-
	4	1	-	-	-	-	-	-	1	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	7	3	1	-	-	1	-	1	1	-	-	1	1	1	1	-	1	-	-	1	2	1	2	-	1	2	2	-	-	1	1	1
Aug.	1	3	-	-	2	1	1	2	1	3	1	-	-	-	2	2	2	1	1	1	2	-	2	-	-	2	-	1	1	-	-	-
	2	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	1	-	-	-	-	-	1	-	-	-	-	-	-	1	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	2	1	1	-	-	-	-	-	-
	6	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	7	3	1	1	1	-	2	-	-	-	1	-	1	1	3	3	1	-	-	-	1	-	1	-	1	1	1	-	-	1	2	-
Sept.	1	2	1	2	1	-	-	-	-	1	-	-	-	1	-	2	1	2	-	-	-	1	7	-	-	-	-	-	-	1	-	-
	2	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	-	1	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-
	5	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6	-	1	-	-	-	-	2	-	-	2	-	-	-	-	-	-	1	-	1	1	1	-	-	-	1	-	-	-	-	-	-
	7	1	1	-	1	-	1	-	-	-	1	1	-	-	1	-	-	-	-	1	2	2	-	1	-	1	2	-	1	2	-	-
Oct.	1	1	1	-	-	2	-	3	-	-	1	-	1	2	1	-	-	-	-	-	-	1	-	-	2	-	1	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	2	-	-	-
	4	1	-	1	-	-	-	-	2	-	-	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-
	6	1	-	-	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-
	7	3	-	-	-	-	-	2	2	4	-	3	-	-	-	1	1	1	1	-	1	-	-	1	-	1	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nov.	1	1	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	1	-	1	-	-	-	-	-	2	1	-	-	-	-
	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	1	-	-	-	-	-	-	1	-	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6	-	-	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
	7	2	-	1	-	4	-	-	1	-	-	-	1	1	-	-	1	1	-	3	1	-	-	-	-	-	-	-	-	1	-	-
	8	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dec.	1	-	1	-	-	-	-	2	-	-	-	-	-	-	1	1	-	-	1	-	1	-	-	-	-	-	-	-	-	-	-	-
	2	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	5	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	7	4	-	-	-	1	1	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Typhoid Studies 1914-15 - H.E.V.

FIG. 15 C.

Clair by Prof. Gardner S. Williams and Mr. C. W. Hubbell in 1897. A ten foot tunnel, 3,000 feet long, connects the crib with the settling basin. This intake was put in operation in December, 1905, and has been in use practically continuously, the old intake being used only in case of extreme necessity.

Source of Pollution of Detroit's Water Supply.

The water-shed draining into the St. Clair River, Lake St. Clair, and the Detroit River, above the intake, has an area of 5,800 square miles, all of which is very thickly populated. The runoff, owing to the nonporous character of the soil, finds its way quickly to the main water channels, carrying with it its load of surface pollution. Prof. Williams estimates that 1½ inches of rainfall furnishes run-off equal to 20 hours' normal flow of the river past Detroit. The entire sewage of Port Huron and other bordering cities is discharged, untreated, into this drainage system.

The danger from the distant sources is minimized to a large extent by two natural agencies—dilution and sedimentation in Lake St. Clair. The amount of water available for dilution is enormous, and the oxidation resulting must be very extensive. Sedimentation also must play a very important role as is evidenced by the formation at the mouth of the St. Clair River. The two most imminent dangers, no doubt, are the pollution furnished by Connor's and Fox Creeks, and that furnished by Lake Commerce. The danger from the former sources is greatest in times of freshet in the creeks. Increased building operations in this direction, more especially dredging operations, are a potent menace to the water supply.

The U. S. Weather Bureau Observer reports two instances in the last 30 years, in which the velocity of the Detroit River has been as great as two miles per hour in a direction opposite to the normal flow. The effect of such a phenomena will be obvious.

In the year 1913, 37,473 vessels used the Detroit River; not all of these, however, contributed to the pollution in Lake St. Clair. Figures based upon the relative amounts of freight passing Detroit and the St. Clair Flats Canal, show that probably about one-fifteenth of the vessels stop at Detroit, and that about 35,000 use the St. Clair Canal, and hence contribute additional pollution.

The pollution from these two sources is not subject to the natural purification agencies to the same extent as that of the cities, towns, and more distant streams. It is therefore to be considered as a menace to our water supply. A study of the data available may disclose to what extent it is an actual danger.

Quality of Detroit's Water Supply.

Early records of the quality of Detroit's water supply are given under the Report of the General Superintendent of the Water Board for the year 1897. The report is a quotation from the Board of Health analyst as follows:

> The importance of a pure water supply to the public health of a community cannot be overestimated. There have been reported from various localities innumerable instances of epidemics traced to the use of a dangerous drinking water. In fact, so numerous are such cases, and so conclusive the evidence pointing to the source of the trouble, that the health authorities of many large cities, appreciating the value of a watchful and preventative policy, have provided for frequent analysis of the public water.
>
> During the past year I have devoted as much attention as possible to our supply, and while the time was not available for as many examinations as seemed desirable, yet several have been made, the results of which, with a brief explanation are here given:

BACTERIOLOGICAL AND MICROSCOPICAL ANALYSIS.

April,	1896.	Bacillus typhi abdominalis (typhoid fever bacillus)	absent
"		Bacillus coli communis	absent
"		Bacteria per cubic centimeter	140
		Microscopical—Fine sand, diatomes and algæ	...
July 9,	1896.	Bacteria per cubic centimeter	95
" 15,	"	" " " "	110
" 18,	"	" " " "	80
Sept. 22,	"	" " " "	200
" 23,	"	" " " "	130
" 28,	"	" " " "	80
Oct. 27,	"	" " " "	40
" 28,	"	" " " "	108
" 30,	"	" " " "	48
" 31,	"	" " " "	130
Dec. 15,	"	" " " "	120
" 16,	"	" " " "	350
" 23,	"	" " " "	85
" 24,	"	" " " "	125
" 29,	"	" " " "	180
" 30,	"	" " " "	180
Feb. 15,	1897.	" " " "	80
" 16,	"	" " " "	800
" 17,	"	" " " "	320
" 18,	"	" " " "	220
" 19,	"	" " " "	480
" 20,	"	" " " "	530
" 22,	"	" " " "	210

The samples were taken from the laboratory tap and subjected to the usual examinations and sanitary and chemical analysis, which includes an estimation of such substances as are of value in determining the drinking quality of the water. The estimation of the number of bacteria is self-explanatory. Good drinking water should not contain more than 1,000 bacteria in each cubic centimeter (about 16 drops).

With the placing of the intake in the main current of the river, in 1905, it was thought that the best available supply was being obtained, and it is reasonable to assume that the quality of the water furnished from this source was materially improved. There is no authentic date, however, relative to the quality of the supply, but we must assume that it remained practically satisfactory until the latter part of 1912 and the spring of 1913, when suspicion was directed toward the water supply by a high typhoid death rate. Because of the situation at this time the Water Board installed apparatus for the addition of calcium hypochlorite to the water. This treatment was begun on April 2, 1913, with the addition of five pounds per million gallons, which was later increased to nine pounds per million gallons in June, 1913. Fig. 16 shows the typhoid death rate by months for the years 1913-1915, inclusive. The arrow indicates the point at which hypochlorite treatment was started. Attention is called to the increase in the typhoid death rate even after sterilization was practiced.

Fig. 17 shows the extent of the B. Coli pollution in the raw and tap water for the last eighteen months. The total instances of typhoid, and the percentage for which the information was not sufficient to assign any specific source of infection is shown above for comparison. There seems for this period to be no direct relation between the number of cases assignable to any specific source and the quality of either the raw or treated water.

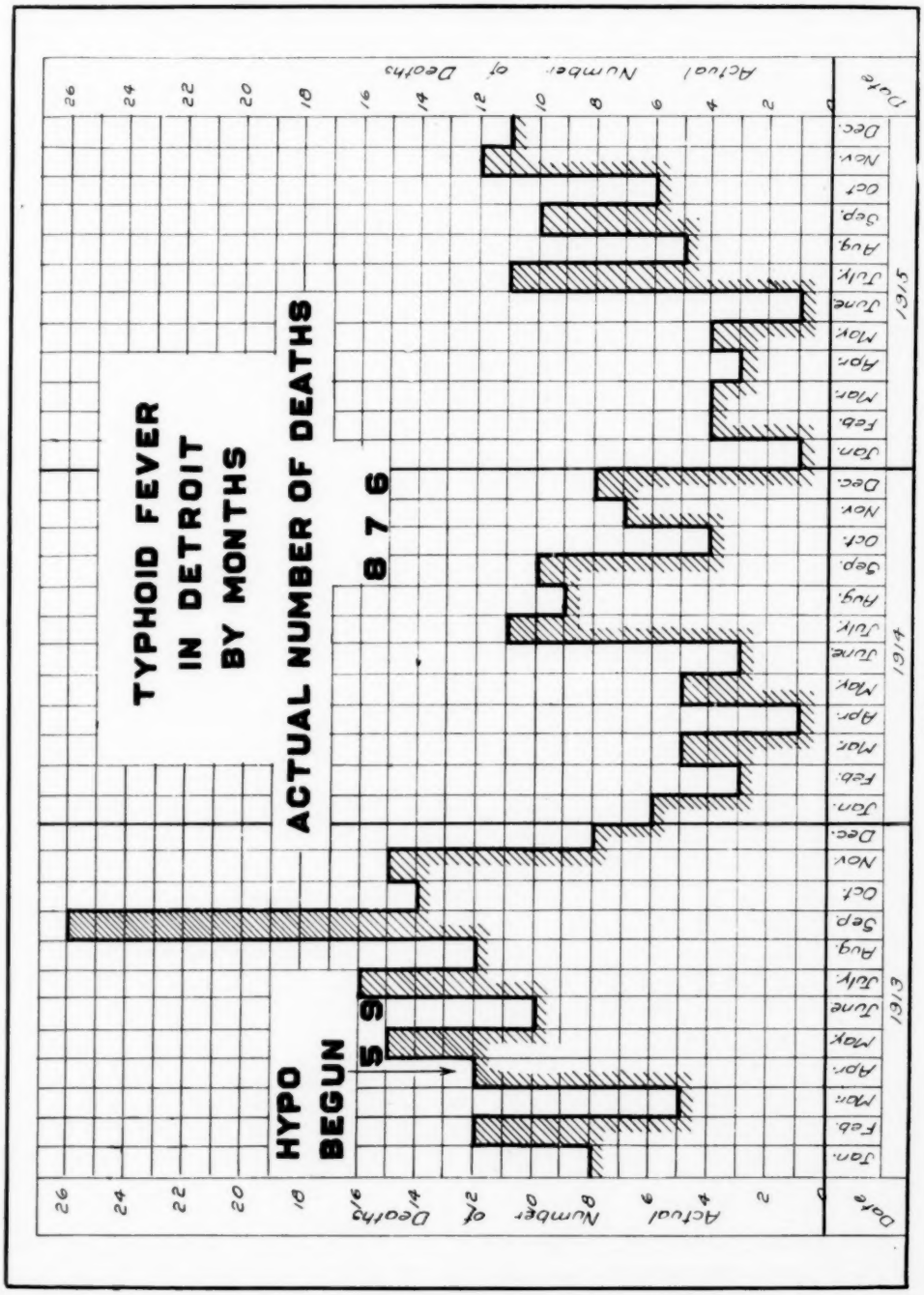

FIG. 16.

Fig. 18 compares the percentage of yearly deaths by months for the last six years with the mean monthly temperatures for the same period. Rather close agreement is shown, in general, between these two curves; two instances may be noticed, viz., April, 1912, and April and May, 1913, when the divergence would lead one to believe that the water supply might possibly be contaminated.

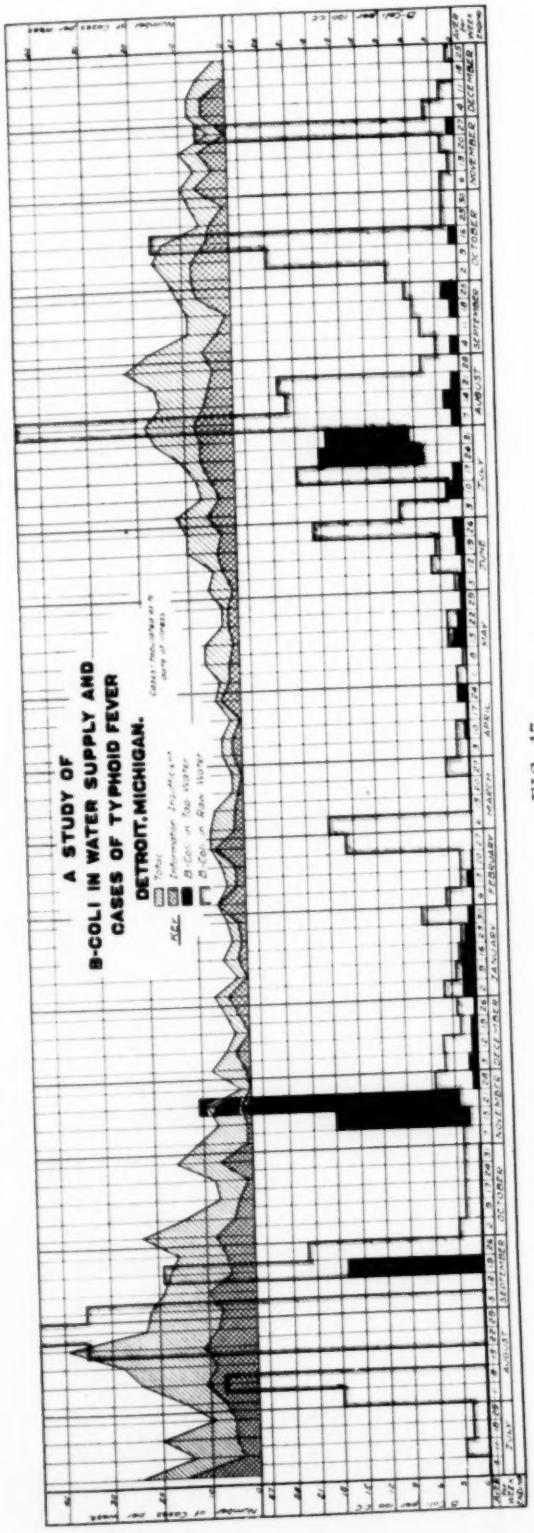
A STUDY OF
B-COLI IN WATER SUPPLY AND
CASES OF TYPHOID FEVER
DETROIT, MICHIGAN.

FIG. 17.

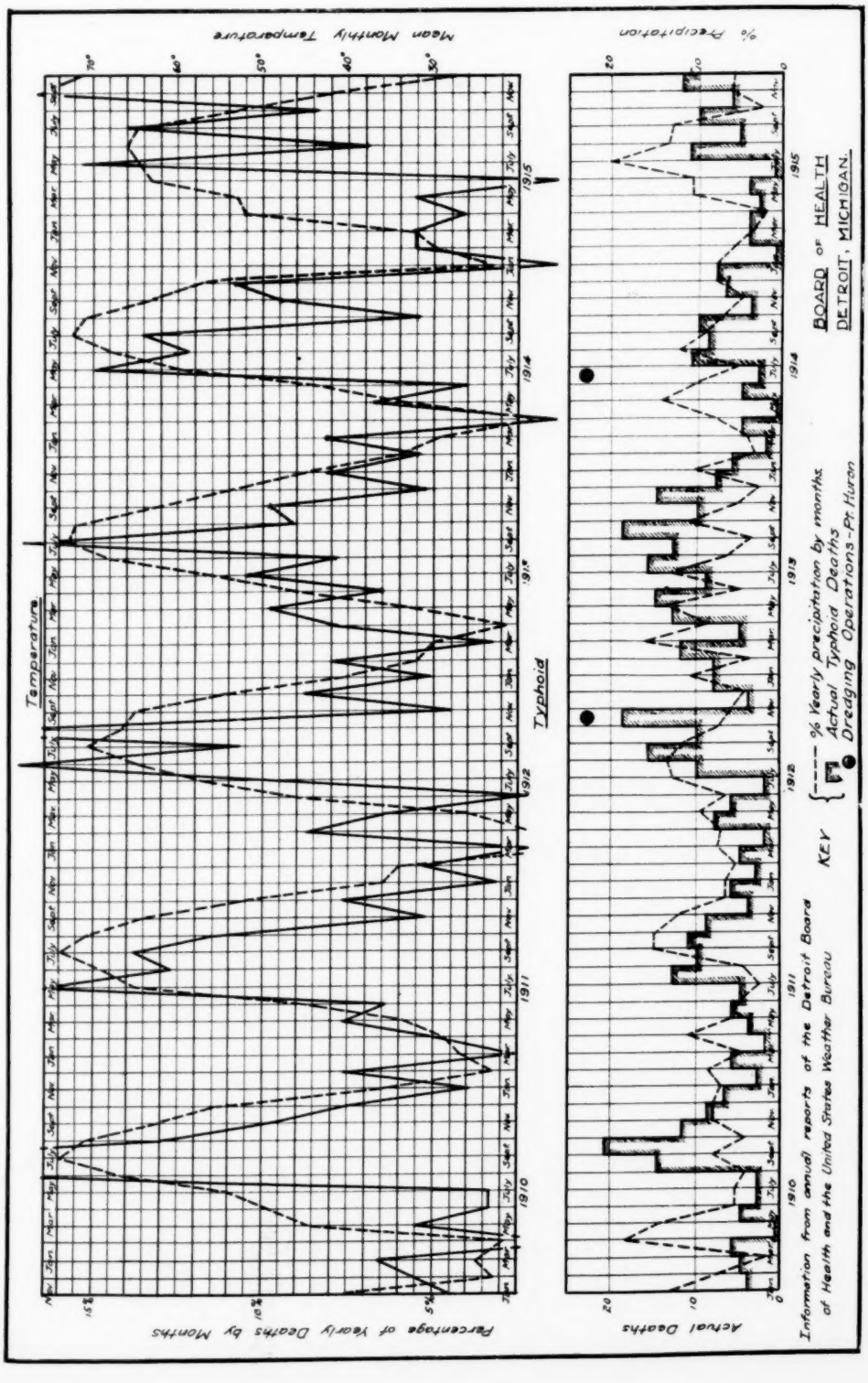
Temperature
Typhoid
Mean Monthly Temperature
Percentage of Yearly Deaths by Months
% Precipitation
Actual Deaths
1910
1911
1912
1913
1914
1915
Information from annual reports of the Detroit Board of Health and the United States Weather Bureau
KEY
---- % Yearly precipitation by months
Actual Typhoid Deaths
Dredging Operations - Pt. Huron
BOARD OF HEALTH
DETROIT, MICHIGAN.

FIG. 18.

On the same chart (Fig. 18) the actual deaths from typhoid are compared with the percentage of precipitation by months.

The use of calcium hypochlorite as a sterilizing agent has been strongly criticised in the city, because of the taste resulting from its use. It is hoped that this objection will be overcome by the use of liquid chlorine, as it is the history of such sterilization that larger amounts of liquid chlorin may be used without imparting an objectionable taste to the water. The change from calcium hypochlorite to liquid chlorine is being gradually made at the present time.

Detroit Sewerage System.

Reference to Fig. 1 will show the location of the sewer outfalls of the city. They number about 50 and discharge the sewage into the river without treatment. The sewage from the district above the intake is collected in an intercepting sewer on Jefferson Avenue and discharged into the river below the intake, at the Fairview Sewage Pumping Station. There are, however, instances of sewage being discharged into Connor's Creek. The one most worthy of note is a factory, which is located inside the city limits, and discharges the sewage from 1,000 workmen, together with other factory wastes, into the creek. This is only of recent origin, and steps have been taken to alter the condition.

The entire Connor's Creek Drainage Basin is rather more densely populated than any of the other contributory basins. The portion just to the north and west of the village of Highland Park being practically all platted, there are several instances in which crude sewage is discharged into county ditches which are a part of the Connor's Creek drainage system.

Fig. 2 shows the extent to which the sewage of Detroit affects the general quality of the water in the river below Detroit. The pollution is so great as to render the use of the river, below Detroit, as a source of water supply dangerous, except after very careful and extensive purification. The typhoid death rates of the towns of Wyandotte, Trenton and Monroe, are relatively high, and, no doubt, this gross pollution of the waters adjoining the down river towns and summer resort district is responsible for an appreciable portion of Detroit's deaths from typhoid fever.

Municipal Refuse.

The refuse of the city is collected by the Department of Public Works. The garbage and rubbish are collected and disposed of separately. The garbage is required to be kept in proper cans and to be kept free of paper and rubbish. It is collected in all parts of the city at least once in seven days and hauled by one horse wagons to two stations, one at Connor's Creek and Jefferson Avenue East, where it is placed on motor trucks and hauled to the principal station at 24th Street and West Jefferson Avenue, where the garbage is loaded onto cars and taken by rail to French Landing, about 15 miles out of the city, where it is disposed of by a reduction process. The wagons are covered with canvas while being hauled through the streets.

The rubbish is collected in two horse wagons holding about three cubic yards, and is drawn to the various dumps where it is used for filling purposes.

There is always quite a quantity of garbage mixed with the rubbish, which renders the dumps a breeding place for flies. The work of the antifly campaign during the last summer, however, has done much toward improving this condition by bringing about a better separation of garbage and rubbish.

Milk Supply.*

Previous to the year 1910, several outbreaks of typhoid fever occurred in Detroit due to infected raw milk. These outbreaks usually gained considerable headway before being discovered, there being no system employed whereby the cases came to the attention of the Health Department until several deaths from typhoid occurred in one locality.

Up to this time the most notable outbreak of milk-borne typhoid occurred during the year 1908. At this time an east side milk dealer was noticed to have a number of cases appearing among his customers, after several deaths had occurred. A canvass of his milk route was made by inspectors of the Board of Health and over one hundred cases found. This dealer was drawing most of his milk supply from farms adjoining Connor's Creek. Investigation of these farms showed that nine were housing typhoid patients. The milk from these farms and all others directly bordering on this creek was excluded from the city. The milk dealer's premises and all his appliances and utensils were very thoroughly disinfected and sterilized before he was again allowed to distribute milk.

Connor's Creek was found to be very badly polluted with sewage, it being a natural drain for the east end of Wayne County. Practically all farms bordering on this creek used it for watering their live stock.

Other outbreaks occurred from time to time up to the year 1910, but were always checked before they gained any considerable headway.

During the year 1910 the milk inspection division was reorganized and the number of inspectors increased. At this time new regulations were adopted, requiring the milk dealer and milk producer to notify the Health Department of any contagious disease which might exist in his family or in that of his employees, or on any of the farms from which he drew his daily milk supply.

Through the cooperation of the dealers and producers no more explosive outbreaks occurred until the summer of 1914, when a milk dealer, vending milk in the city from a dairy outside, deliberately concealed a case of typhoid fever in his family. The patient was removed to a city hospital, from which place the case was reported. On investigation, the visiting nurse was informed by the patient that she had come in from the country and that her people were not engaged in the milk business. About this time other cases were being reported and charged against this milk dealer, the father of this patient. Further investigation by the milk inspection division revealed the above facts. The dealer was eliminated from Detroit, leaving a trail of eighty cases of typhoid and six deaths.

Shortly after this outbreak all milk sold in Detroit was ordered pasteurized. Since the enforcement of compulsory pasteurization May 1, 1915, no cases of

*We are indebted for the following information to Mr. Krehl, Chief Milk Inspector, Detroit Board of Health.

typhoid or other contagious disease have been traceable to the milk supply. However, milk dealers and producers are still obliged to report contagious diseases as mentioned above.

Factory Water Supplies.

In the spring of 1914 the attention of the Health Department was attracted by the large number of typhoid cases reported among workmen at one of the large river front factories. An investigation developed the following points as shown diagrammatically in Fig. 19.

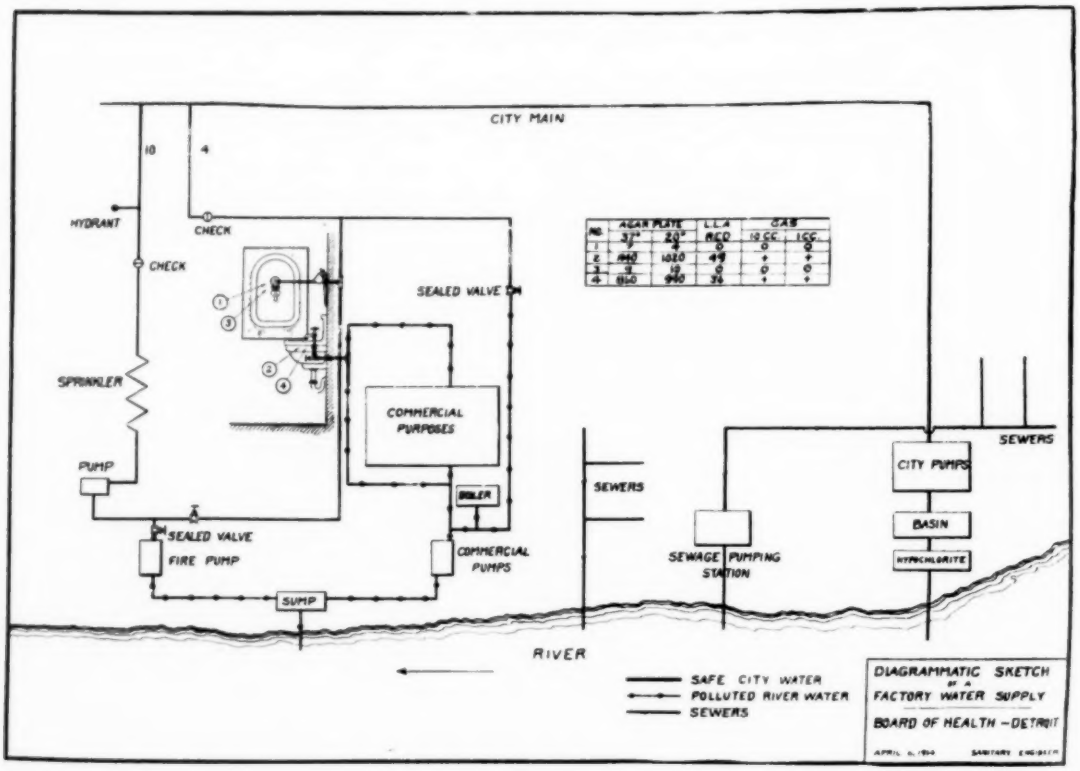

FIG. 19.

The factory in question was using raw river water for boilers, washing rolls, flushing toilets, lavatory, and on the sprinkler system. As is shown in the chart, the relative position of the drinking fountain tap, supplied with city water, and the lavatory, supplied with river water, was such that workmen could easily use the river water for drinking purposes, if for any reason the city supply was not easy of access, there being nothing to indicate that one was suitable and intended to be drunk, and that the other was grossly polluted. Moreover, the very use of the river water in the lavatories constituted a danger and a menace to the health of the employees, as it is only a short time when the typhoid bacilli are on the face and hands until they are in the mouth and into the alimentary canal.

The finding of this condition was the beginning of a survey which included

all the river front factories, which were drawing any part of their water supply from the river, and the subsequent issuing of an order, based upon the results of this survey, to the effect that wherever water was used in such a manner that the workmen must come into intimate personal contact with it, the water must be of a quality equal to that furnished by the city main. The manufacturers have been quick to see the need of such a measure, and compliance is practically unanimous, although some time is needed to complete the alterations in piping made necessary, the cost being estimated in some instances to be three and four thousand dollars.

Water Supply of Boats.

The passenger boats operating out of Detroit carry annually, approximately 10,000,000 passengers; about six million of these are carried on those boats termed "ferries," and operating wholly within the Detroit River, between Detroit, Belle Isle and Windsor. The boats carrying the remaining four million operate in the river, and the lakes and rivers adjoining it on either end.

A survey by the Health Department, during the summer of 1914, proved beyond doubt, that the water supplied to the passengers for drinking purposes, on all the boats operating out of Detroit, was far below that standard of bacteriological purity which indicates a safe drinking water. At the time of the survey, the boats were, without exception, drawing their supply from the lake or river water through which they passed, and were supplying it to their passengers without treatment.

Fig. 20 shows diagrammatically the general arrangements for supplying drinking water as they were found at this time. The fresh-water storage tanks were filled by the general service pumps, when the boat was in the best water attainable. There was always the danger that the pumps had been contaminated by the water drawn in while laying at docks, and that this contamination still remained to further pollute the supply. Then, too, there is the possibility of leaking valves, which might allow water to pass into the freshwater tank when the decks were being washed, or when the trim tanks were being filled; no instance being found in which there were two valves on the same line with a drain between.

It was shown by the Progress Report of the International Joint Commission in reference to the Pollution of Boundary Waters * * * Date of January 16, 1914, that in all instances, the lake and river waters traversed by the vessels, considered here, were of such character as to be rendered suitable for drinking purposes only after extensive purification.

Upon completing this survey, the different navigation companies were notified of the results, and the conditions as they existed on the boats in question were pointed out, it being plainly demonstrated that it was to the ultimate advantage of the navigation company to supply its patrons with a safe water. Assurance was given that full cooperation might be expected from the Health Department.

Because of the peculiar conditions affecting the purification of water on boats, the Health Department did not feel in a position to dictate as to how the purification should be brought about; but simply maintained the policy that water

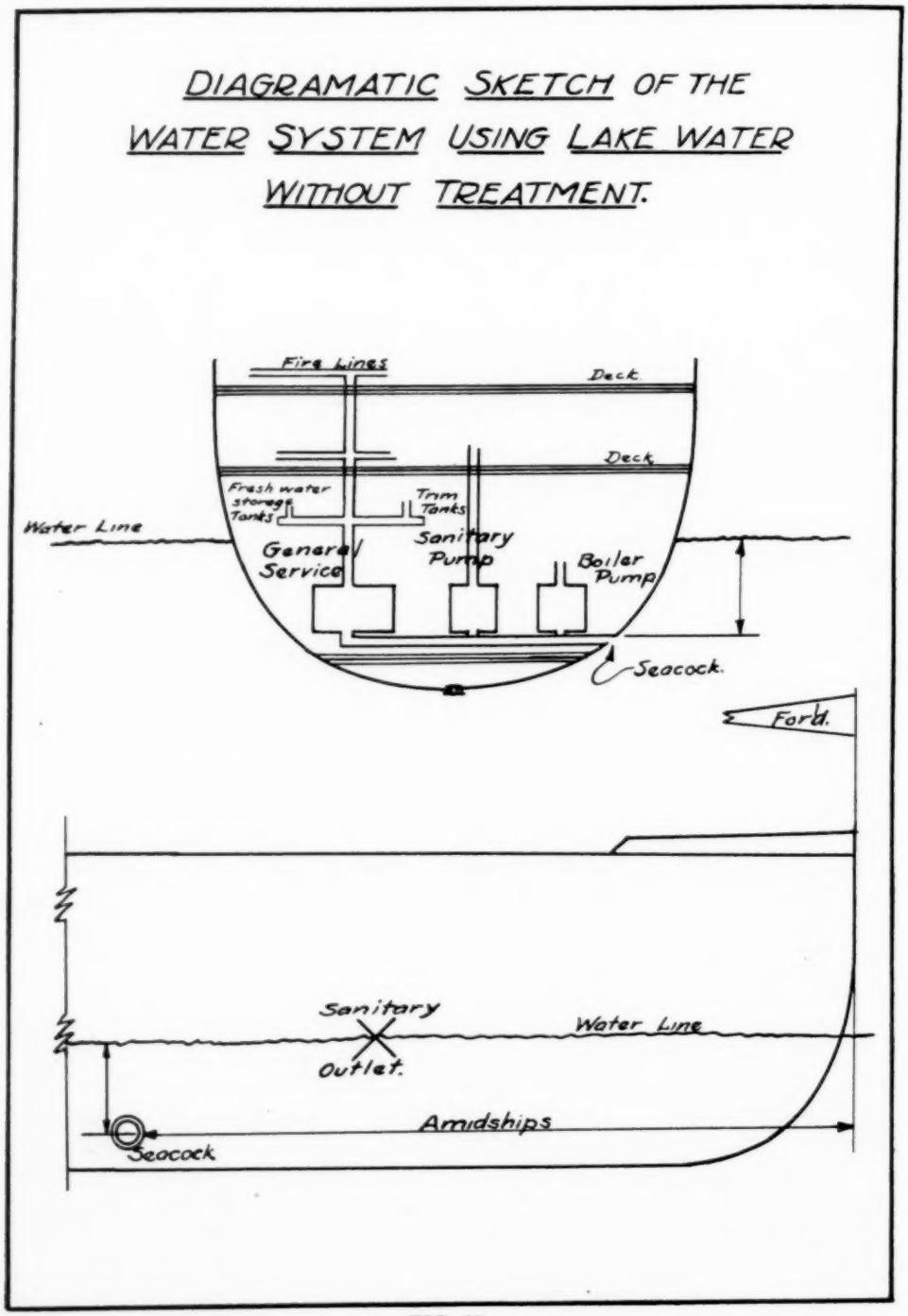

FIG. 20.

was to be considered safe which came within the limit of permissible impurity established by the Treasury Department, that is to say, the water supplied for drinking purposes must not show the presence of more than 100 organisms per

cubic centimeter when plated on standard agar and incubated for 24 hours at 37°, nor may it show the presence of the Colon Bacillus in more than one of five 10 c.c. portions by the fermentation of standard lactose broth within 48 hours at 37°, and the subsequent confirmation of the same on Endo's media and by refermentation. This desired end was sought by four distinct methods, viz.:

1. Taking water from city mains.
2. Taking lake water and filtering by a rapid sand filter.
3. Taking lake water, filtering by a rapid sand filter and treating the effluent by liquid chlorine.
4. Taking lake water and sterilizing it by means of live steam under pressure.

Fig. 21 shows the results of analyses of samples of water by *Method No. 1*, collected during the past season. These boats drew their supply from a 2 inch line on the dock, using a hose connection to fill the tanks located in the hold. The high count in these samples is undoubtedly due to incubation in the tanks, the temperature being usually between 85 and 90° F. Samples of tap water left standing at room temperature for a period of 24 hours showed an increase in the count as follows:

Original count, 13; final count, 2,400;
" " 75; " " innumerable.

This seems to indicate that the high count was simply a multiplying of those forms already in the water. Sterilization of the tanks by a hot solution of calcium hypochlorite was recommended as a preventive measure.

Method No. 2 consists in the application of the pressure type of rapid sand filter. The first difficulty encountered in this method of purification was to find a place in which to put the filter. It was finally located in the engine room near one of the cylinders. The same condition of high temperature also obtains here.

Fig. 22 shows the total bacterial count in all the samples taken since the first of the season. A remarkable decrease toward the last is due largely to the untiring efforts of the engineer in charge, in cleaning and sterilizing both the lines and storage tanks.

Fig. 23 gives the colon content, as well as the count, for the latter part of the season. Due to the change in the method of analysis, the record of the B. Coli for the whole season is not directly comparable. It is evident, however, that even with the exercising of great care in the operation of a rapid sand filter, it cannot be relied upon to furnish a safe water when the character of the source is such as the boat in question traversed during the past season. The failure to supply water of a suitable character is probably due to high temperatures surrounding the filter and inability to wash the filter with filtered water.

Method No. 3 consists in filtering lake water through a rapid sand filter and treating the effluent with liquid chlorine. The same difficulties were encountered in the operation of the filter in this instance as occurred in the one already discussed.

The liquid chlorine is used to make up a solution of chlorine water of known strength, which in turn is fed into the main supply pipe in quantities propor-

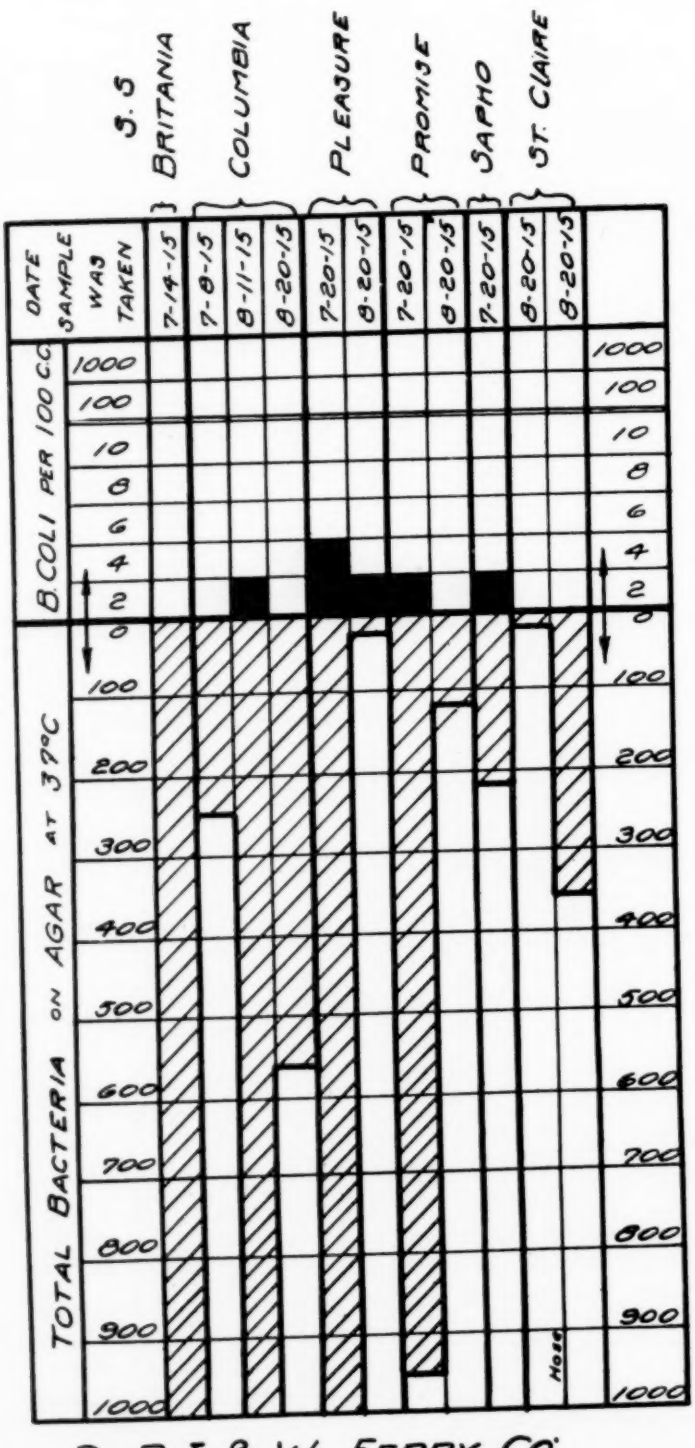
S. S BRITANIA
COLUMBIA
PLEASURE
PROMISE
SAPHO
ST. CLAIRE
DATE SAMPLE WAS TAKEN
7-14-15
7-8-15
8-11-15
8-20-15
7-20-15
8-20-15
7-20-15
8-20-15
7-20-15
8-20-15
8-20-15
B. COLI PER 100 CC
1000
100
10
8
6
4
2
0
TOTAL BACTERIA ON AGAR AT 37°C
100
200
300
400
500
600
700
800
900
1000
HOLE
D, B I & W FERRY CO.

FIG. 21. D.F.

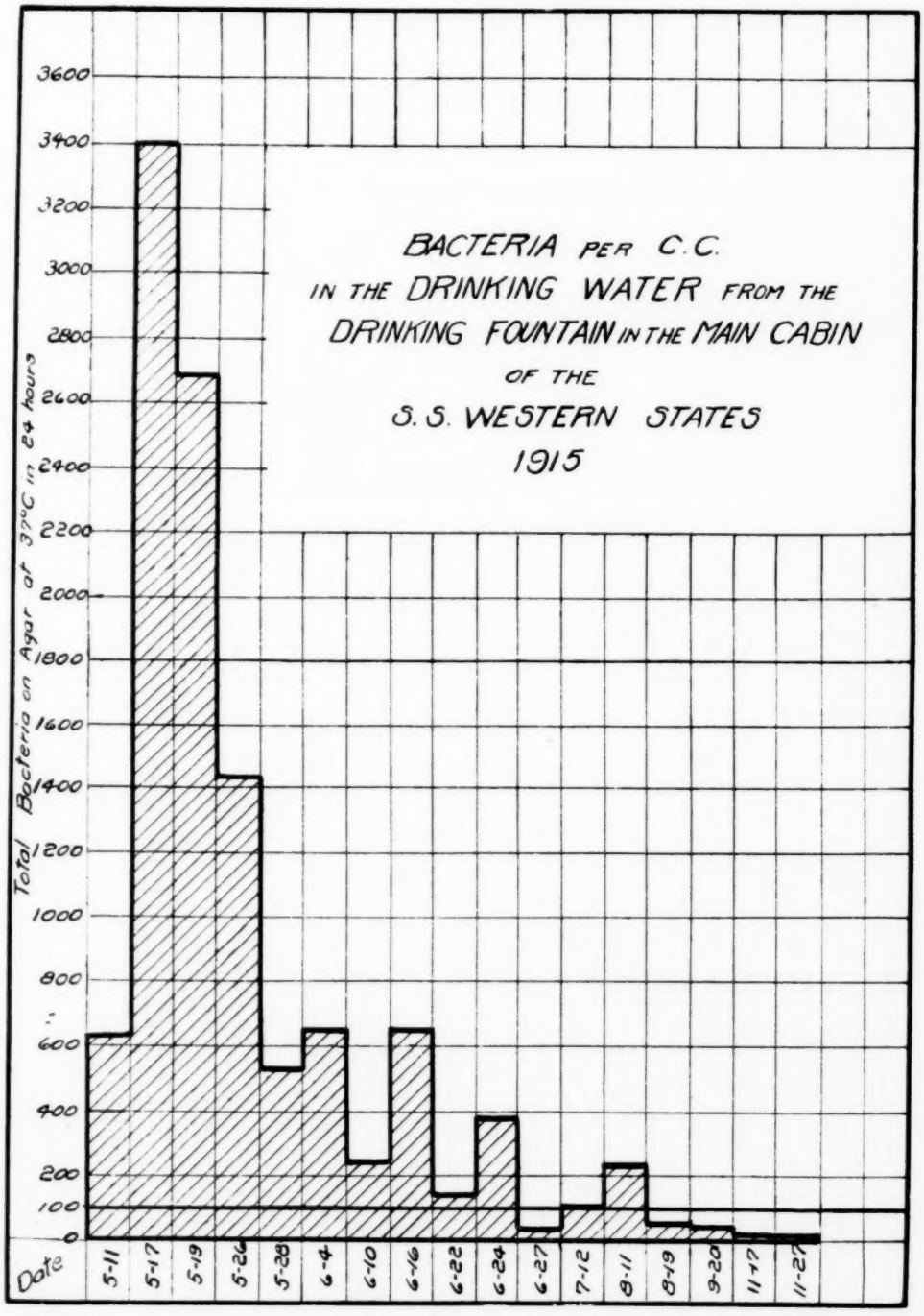
BACTERIA PER C.C.
IN THE DRINKING WATER FROM THE
DRINKING FOUNTAIN IN THE MAIN CABIN
OF THE
S. S. WESTERN STATES
1915
Total Bacteria on Agar at 37°C in 24 hours
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
100
0
Date
5-11
5-17
5-19
5-26
5-28
6-4
6-10
6-16
6-22
6-24
6-27
7-12
8-11
8-19
9-20
11-17
11-27

FIG. 22.

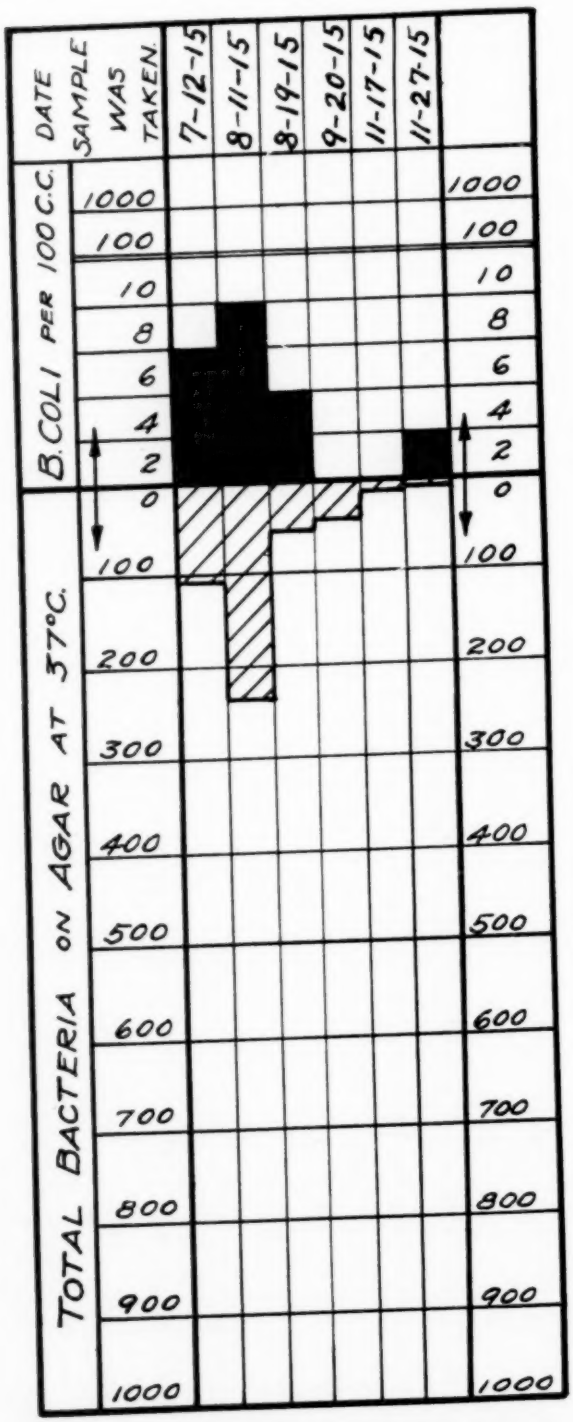
DATE SAMPLE WAS TAKEN
7-12-15
8-11-15
8-19-15
9-20-15
11-17-15
11-27-15
B. COLI PER 100 C.C.
1000
100
10
8
6
4
2
0
TOTAL BACTERIA ON AGAR AT 37°C.
100
200
300
400
500
600
700
800
900
1000
S.S. WESTERN STATES.
D.F.M.C.

FIG. 23.

tional to the demand, by means of a shunt feed around a constriction; being an application of the Venturi principle, one charge of chlorine being sufficient for about four days' use.

Fig. 24 shows the results obtained by this method. Examination of the results in the first column shows that the general character of the raw water was very low, while in only three instances does the final product fail to meet the requirements of the standard. From the results obtained, it would seem at first glance that this method would be one worthy of consideration, but further investigation discloses that the operation of the chlorinating apparatus is complicated, and so far out of the line of work of the ordinary engineer in charge of a lake steamer that the chances of its being operated satisfactorily on all vessels are very slight. The duties of the engineer are primarily with his engine, and in the time of crisis, the water supply would be given only little attention, and due to the nature of the chlorine gas serious conditions might arise should the apparatus develop a leak. In the vessel in question a situation quite similar to the above did occur, after one of the hard rubber connections between the absorption chamber and the chlorine water storage chamber had broken during a hard storm. The engineer, in charging the apparatus, had drawn the required amount of gas into the measuring chamber and was about to absorb it when the broken connection was noticed by the escape of gas. The engineer had the presence of mind to turn on the water and flood the room, absorbing the gas and preventing any disastrous results. With a more serious break or a larger quantity of gas, the situation would have been dangerous.

Method No. 4, that of sterilization by steam under pressure, was developed by Mr. Winfield Dubois, Chief Engineer of the White Star Line, and consists essentially of heating the water to a temperature above the thermal death point of the pathogenic organisms contained and cooling it again, maintaining a pressure at all times of five to ten pounds. Inasmuch as the water is not exposed to the air during the time it is heated above the boiling point, there is no opportunity for expelling the entrained gases, so that the treated water does not have the flat taste characteristic of a boiled water.

Fig. 25 shows diagrammatically the device as installed on the Steamer Owana:

A. Injector for drawing water from seacock and forcing it through the system.
B. A jet for introducing live steam under pressure.
C. A tank containing 208 feet of 1½ inch pipe for cooling purposes.
D. Pump for circulating cooling water.
E. Storage tank.
F. and *G.* Control thermometers.
H. Blow-off valve.

When the device is operated the blow-off valve is opened and the system from the steam jet is blown out with live steam for five minutes. The injector is then primed and allowed to pump to waste through the blow-off until the temperature of the water delivered, as shown by Thermometer *F*, is properly regulated by the steam jet. When the desired temperature has been reached the cooling pump is started and the blow-off closed, so that water is delivered into the

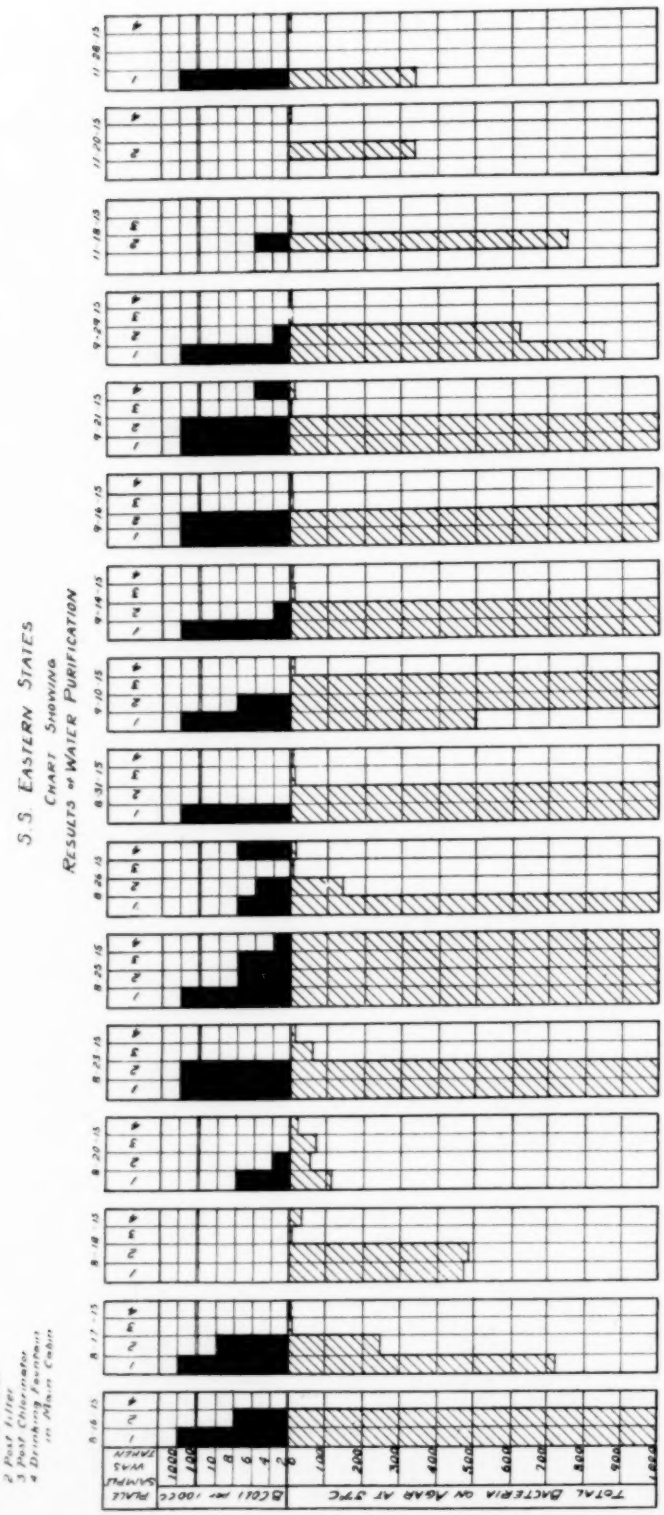
S.S. Eastern States
Chart Showing
Results of Water Purification
1 Raw Water
2 Post Filter
3 Post Chlorinator
4 Drinking Fountain in Main Cabin
Total Bacteria on Agar at 37°C
B Coli in 100 cc
Plate
Sample
Taken

FIG. 24.

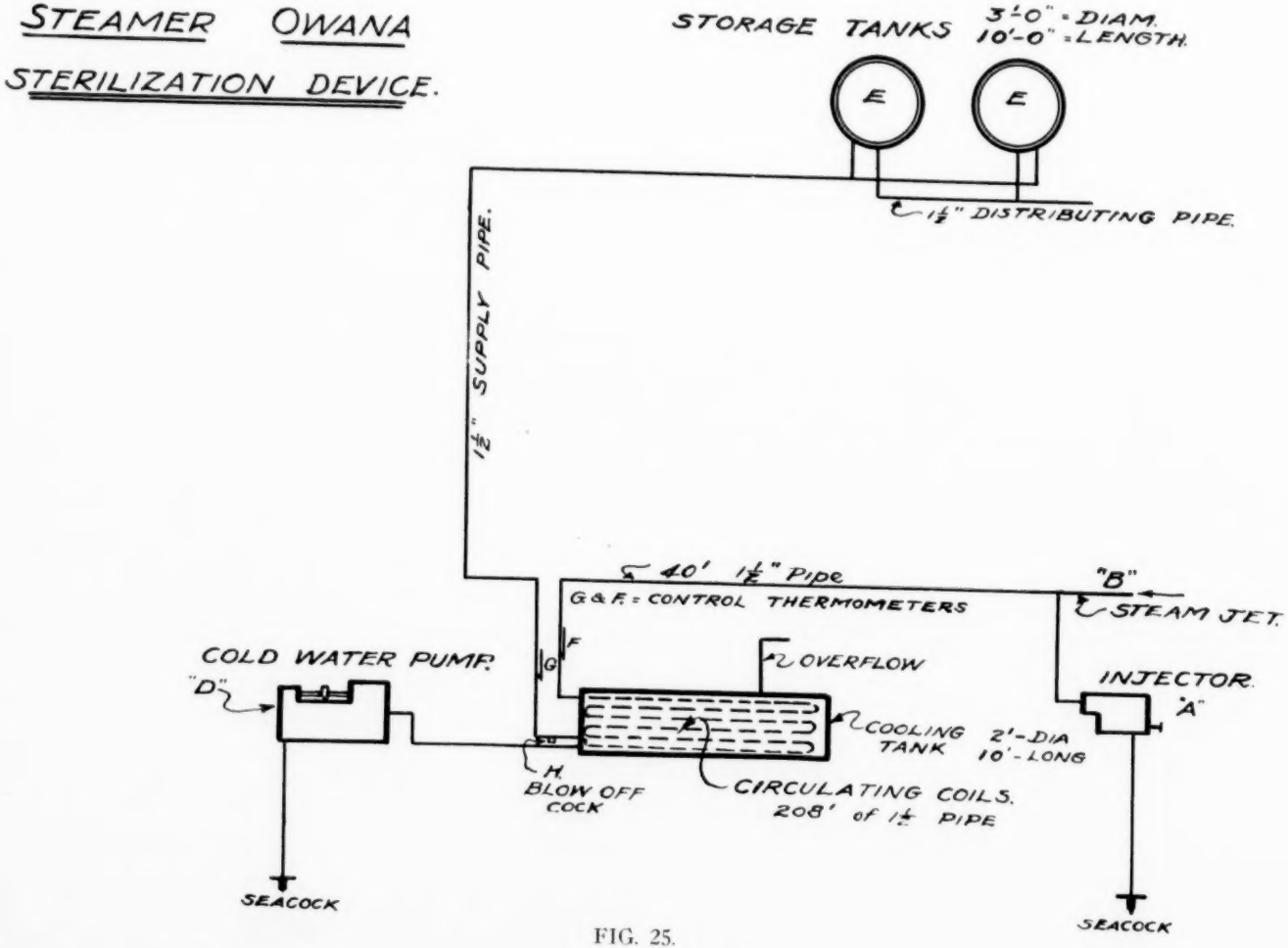
STEAMER OWANA
STERILIZATION DEVICE.
STORAGE TANKS 3'-0" = DIAM. 10'-0" = LENGTH.
E
E
1½" DISTRIBUTING PIPE.
1½" SUPPLY PIPE.
40' 1½" Pipe
G & F = CONTROL THERMOMETERS
"B"
STEAM JET.
COLD WATER PUMP.
"D"
F
G
OVERFLOW
INJECTOR.
"A"
COOLING TANK 2'-DIA 10'-LONG
H
BLOW OFF COCK
CIRCULATING COILS. 208' of 1½ PIPE
SEACOCK
SEACOCK

FIG. 25.

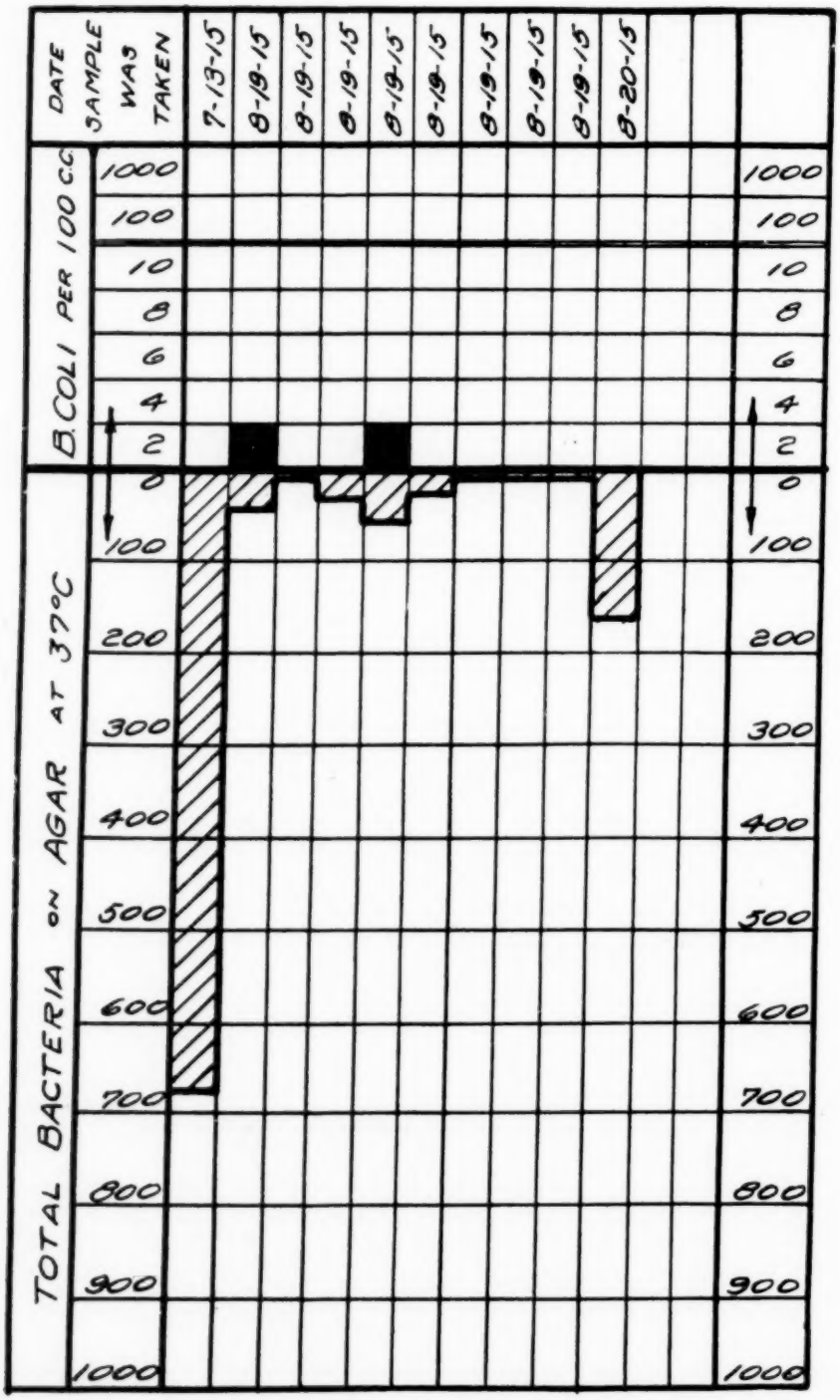
DATE SAMPLE WAS TAKEN
7-13-15
8-19-15
8-19-15
8-19-15
8-19-15
8-19-15
8-19-15
8-19-15
8-19-15
8-20-15
B. COLI PER 100 C.C.
1000
100
10
8
6
4
2
0
TOTAL BACTERIA ON AGAR AT 37°C
100
200
300
400
500
600
700
800
900
1000
S.S. GREYHOUND

FIG. 26.

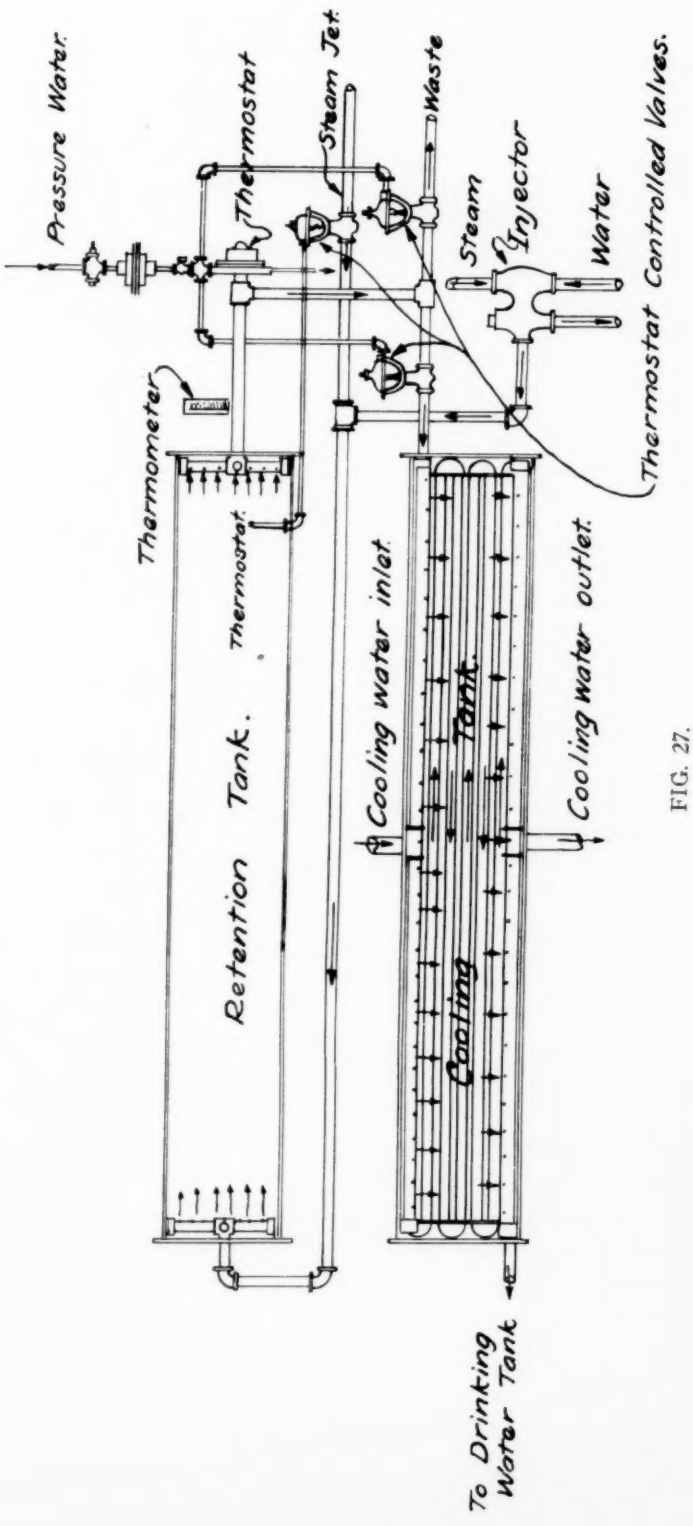
Pressure Water
Thermostat
Steam Jet
Waste
Steam
Injector
Water
Thermostat Controlled Valves.
Thermometer
Thermostat.
Retention Tank.
Cooling water inlet.
Cooling Tank.
Cooling water outlet.
To Drinking Water Tank

FIG. 27.

storage tank. The results of analysis of water treated by this method on a test run of the Steamer Greyhound are shown in Fig. 26.

The results of the first season's work have shown the need of devices for water purification which are automatic and which cannot in any way go wrong. Under the conditions that they must be operated, all of the apparatus must be "fool-proof" in order that at no time may the water be unsafe.

Because of the nature of the method, and the fluctuation in the demand, there seems to be at present no liquid chlorine apparatus which will meet this requirement.

The use of ultra-violet rays as a sterilizing agent was contemplated by one of the lines, but the idea was later abandoned for the following reasons:

1. The wide fluctuation in the voltage of the current on the boats causes the light to go out at each fluctuation and it does not light automatically, thus allowing water to pass unsterilized.

2. Necessity for filtration.

3. Danger of breaking candles, putting the apparatus out of order for an indefinite period.

An attempt has been made to obviate these difficulties in recent design, but it is still in the experimental stage.

Fig. 27 shows the changes made in the steam sterilizer which provide it with automatic control, so that no water may pass into the cooling tank which has not been heated to 220° for five minutes. It is thought that with these changes a nearly sterile effluent may be obtained. This improved device will be used by one line, at least, during the next season.

Laboratory Methods.*

The method of examination of drinking water in the laboratory is that adopted by the American Public Health Association at its last annual meeting. Briefly, it consists of the counting of plates inoculated with 1 c.c. portion of the water, one set being kept at 20° C. and counted after 48 hours; the other after 24 hours at 37°. Smith fermentation tubes are used for presumptive test for B. Coli. Five tubes are inoculated with 10 c.c. of the sample, and one tube with 1 c.c. These tubes are filled with lactose broth media and are incubated for 48 hours at 37°. If any show gas production during this time, portions are removed and streaked on freshly prepared Endo plates. If any of these streaks show a sheen of reduced fuchsin after incubation at 37°, a portion of the growth is inoculated into a second fermentation tube and incubated for 48 hours at 37°. Those tubes showing gas production and which are confirmed on Endo media and again show gas on incubation in lactose broth are counted as showing colon present. An enumeration of colon per 100 c.c. is made according to the Phelps Method. In addition 100 c.c. of water is mixed with concentrated lactose broth and incubated for 24 hours at 37°. Fermentation tubes are inoculated from this enrichment bottle and carried through the usual procedure as above. Fermentation, confirmation on Endo with gas production on refermenta-

*We are indebted to Mr. Roy W. Pryer, Director of the Board of Health Laboratory, for this data.

tion is taken to show the presence of 1 B. Coli per 100 c.c., providing the other fermentation tubes show no gas production.

Routine Milk Examination.

The routine bacterial examination of milk is the enumeration of the number of organisms growing at 37° in 48 hours. Usually two dilutions are made; one, 1-1,000; the other, 1-10,000.

Widals.

Widals are made whenever physicians send in blood for this purpose.

Ordinarily, a few drops of blood are sent in a capillary tube. One part of serum is diluted to twenty parts with saline solution, and this solution is then added to an equal volume of typhoid suspension. Agglutination within one hour in a hanging drop is reported as a positive Widal. In many cases the test is made using paratyphoid a and b, as well as Bacillus Typhosus.

Conclusions and Recommendations.

1. In view of all facts in connection with the situation it seems apparent that Detroit's typhoid during the past eighteen months has not been due to the unusual operation of a single factor but rather to the combination of several factors, each working independently of the other and one being more active at certain times than another.

2. It is evident that doctors have been somewhat at fault in their diagnosis. The laboratory department is now making every possible effort to cultivate the physicians and assist them by making Widals or other desired tests.

3. Milk infection has in the past been responsible for a marked percentage of typhoid cases but it is hoped that compulsory pasteurization will materially decrease the percentage of cases due to this source and it is thought that the compulsory physical examination of all employees who handle the milk after pasteurization would practically perfect the public protection.

4. Contact probably has played a more important part in the spread of typhoid infection in Detroit than any other single factor. The elimination of cases from this source of infection depends upon the widespread dissemination of knowledge concerning the cause and prevention of this disease and the strict enforcement of existing sanitary regulations.

5. Boats, freight and passenger, have added their share of cases. Too much emphasis cannot be laid upon the necessity of procuring and analyzing samples of water from each boat stopping at Detroit, the source and method of handling the water being equally important.

6. The presence of gross pollution along the river front is directly detrimental to the health of the citizens.

(a) Possible pollution of municipal supply.
(b) Pollution of factory supplies.
(c) Pollution of bathing beaches and other means of direct contact with river water.
(d) Cases of infection from river water imported from neighboring communities.

The elimination of this unwarranted river pollution should be effected by the adoption of proper sewerage and sewage treatment for the city and the compulsory sterilization of all sewage emanating from lake commerce.

7. Dr. Wm. H. Price in his annual report for 1914 states:

"Detroit may be said to have been more fortunate than otherwise in having limited typhoid to the present rate when all circumstances are considered. That the element of fortunate circumstances may not be overloaded, due attention should be directed toward purification of the present water supply."

The treatment of the municipal water supply by an oxidizing agent, such as hypochlorite of lime, liquid chlorine or a similar agent, should, at its best, be considered only as a temporary expedient. It is our opinion that in no case does a surface water which receives drainage from a territory occupied by human inhabitants or used for agricultural purposes, form a safe and satisfactory source of drinking water without some form of treatment or purification. Immediate steps should be taken to obtain for Detroit a water supply which will, without question, be clean and safe at all times.

8. The carrying out of the foregoing recommendations can probably best be brought about by the establishment of a sanitary district of sufficient size to include the drainage areas immediately affecting the local problems.

IMMUNITY IN TUBERCULOSIS

By Gerald B. Webb, M.D., Colorado Springs, Colo.

A COMBAT through almost countless generations with the tubercle bacillus has left most branches of the human race with a remarkable power of resistance to the parasite. We cannot claim, however, that we have any absolute immunity to the disease tuberculosis. On the contrary, tuberculin tests and postmortem records point to the probability of everyone having had at some time some degree of infection with this wax-coated bacillus.

Natural Immunity.

We know of no animal race or human race which is not or cannot be infected with tubercle. Tuberculosis has been found occasionally in wild animals. —lions, tigers, panthers, jaguars.

Cattle would seem to have a relatively greater immunity to the bovine bacillus than man has to the human. In fact, Theobald Smith[1] has said that he believed cattle were nearly immune. This is borne out by statistical evidence. We find that practically each member of the human race is or has been infected with the tubercle bacillus, whereas from records kept at slaughter houses, the percentage of cattle infected varies from 15 to 35 per cent. The percentage of other animals found infected has been noted as follows: hogs 2.5 per cent, sheep and goats .1 per cent. The opportunity for infection must however be considered.

Gray mice are, it is thought, immune to both the human and bovine strains and only once was a softened focus found in experiments conducted by Theobald Smith.[2] Wells' experience corroborates this. The white or albino mice, however, can readily be inoculated with bovine tuberculosis, and field mice are very sensitive.

Spontaneous tuberculosis has been observed in carp, snakes, turtles and frogs. The bacillus affecting such cold-blooded animals will however not cause a general disease when inoculated into the warm-blooded species.

It is not yet settled that tubercle bacilli from warm-blooded animals can infect cold-blooded animals.

Parrots apparently can be infected with either avian, human, or bovine bacilli.

The hedgehog has been found to be a very resistant animal to infection.

Local lesions can of course be produced in any species by the inoculation of bacilli of other types. But such can be obtained by the dead as well as by the living, and Petruschky[3] explains these lesions as being due to the irritating cell toxicity of the bacillary bodies.

According to Sofer,[4] "The phthisical tendency is diminished for the northern race, just as the apoplectic tendency is for the Alpine, brachycephalic race."

No race of man which has had opportunity for infection has escaped. Tuberculosis of the spine has been observed in Egyptian mummies of the periods 3500 B. C., 2000 B. C., and 1500 B. C. In modern Egypt, however, tuberculosis was unknown. It has reappeared in Egypt and Palestine within the memory of physicians practicing there. This has been attributed to the introduction by infected Russian pilgrims, and to the return of native emigrants from America.

In recent years in Scotland and Ireland tuberculosis has spread from the towns to the country, and has become more widespread among the peasants which were formerly fairly free from the disease. As a result of modern rapid communication between various districts and countries, the disease may even become more widespread.

From an analysis of the death rate from tuberculosis, Karl Pearson[5] has shown that, like other diseases, there would seem to be periods of increase and decrease in the prevalence of this disease. As Saundby[6] states, we see this sequence in such diseases as plague, influenza, cholera, and typhoid fever; but the interval of time is short, lasting at most over a few decades. With tuberculosis, it apparently extends over centuries.

It appears that the present is to be considered a period of decline in the tuberculosis death rate, as in the last fifty years a decrease of almost 50 per cent has been observed both in England and America.

It was at one time thought that a certain definite immunity existed among the dwellers of high altitudes. It has been found, however, that this was due to lack of opportunity for infection.

Colorado Springs has a community largely composed of victims of pulmonary tuberculosis. Many of these have married usually healthy consorts, yet not infrequently have there been marriages between tuberculous victims. The writer has observed the children born to such marriages over a period of

twenty years. By means of von Pirquet tuberculin tests it has been found that all these children will react.

An occasional case of tuberculous meningitis and of an acute general tuberculosis has been observed, yet such are extremely rare. An outbreak also of open tuberculosis is exceedingly rare. The infection among these children is usually benign and easily overcome, and compares with that found in the slightly infected among healthy families in the lowlands.

Possible explanations for the disease being benign in this region are the large amount of open air life that is possible, and the increased numbers of lymphocytes the blood contains at such altitudes (Webb and Williams[53]).

Certain families and individuals would seem to have a decided immunity to tuberculosis. Petruschky[3] calls attention to what he designates "mother-immunity." It has frequently been observed that women originating from healthy families have married into a tuberculous family. They have not become infected by their tuberculous husbands, yet their children have one after the other died of tuberculosis. In the cases the writer has observed, the "mother-immunity" has been relative and not complete. Such mothers may react to the von Pirquet skin test, and one such was found to be herself a "carrier."

An inheritance of tubercle bacilli from infected parents is now regarded as being so rare a condition that we need not discuss it here. The so-called "habitus phthisicus" is today believed to be not a condition favorable to tuberculous infection, but a condition resulting from early tuberculous infection.

Neither is there an increased immunity enjoyed by the physically strong, such as athletes over the immunity of the frailer members of the race.

At one time it was considered that the children springing from tuberculous ancestors were less resistant than others, and marriage into such families was condemned.

The late Dr. Solly[7] of Colorado Springs was one of the first (1895) to show that such offspring show more lasting cures and more chronic forms of pulmonary tuberculosis than those who had no tuberculous progenitors. Turban[8] (1899) noted similar condition.

According to Reibmayer,[9] the longer a region is pervaded with tuberculosis, the less becomes the death rate from tuberculosis in spite of the greater distribution of the infection.*

Petruschky believes that the large number of deaths in tuberculous families to be due to (1) the high virulence of the bacilli which have been tuned for that family, (2) the greater opportunity for massive infection, and (3) the earlier infection in childhood.

Children in their first year will almost invariably die from such infection. From year to year thereafter their resistance is increased, but by the school age greater opportunity for infection again takes place, and the mortality again increases. The next period of greater mortality comes at a time of life when the greatest efforts and strains of the bodily power are made and the resistance gained by a mild infection in childhood is over-ridden by a new infection from without or metastasis from within.

*Bushnell, Col. G. E.: Immunity Through Tuberculosis Infection (The Military Surgeon, 1913) contains an excellent review of this subject.

The question of racial immunity must be considered in relation to the opportunity for infection. In countries such as Turkey which was more or less unaffected, Deycke[10] has shown that the importation of tuberculosis has been followed by a severer form and a more acute course of the disease.

Petruschky distinguishes several types of immunity in tuberculosis:

1. Genuine, persistent nonsensitiveness.
2. Different grades of relative resistance.
3. Cellular and humoral changes which can be brought about by immunization.
4. Defensive phenomena of the tuberculous organism.

The Bang system which has been tried in Denmark of breeding from tuberculin-reacting cows, would seem to be succeeding in producing healthy cattle for dairy purposes.

Pathological Processes.

In the invasion of the body by the tubercle bacillus, the parasite strikes out at once for susceptible tissue. We do not find the first lesions in children in muscle tissue for instance, but in lymph nodes.

Ghon[11] believes there is always a primary lesion in the lung and from this the disease spreads to the nearest lymph nodes. Our own experiments with minimum lethal doses would seem to indicate that local lesions would depend on the resistance of the animal and also on the numbers and virulence of the bacilli injected. Natural infection most probably takes place with very few bacilli of varying virulence, and our experiments have indicated that it would be by no means unusual for an animal to escape a local lesion with such minute doses as ten to twenty bacilli.

Theobald Smith[1] states that it is the rule in bovine infection for the lymph nodes to become diseased without there being any lesion at the site of entry of the bacilli. Ravenel[12] showed that tubercle bacilli could pass through the normal intestinal wall. Smith has also pointed out that should bacilli escape from a primary focus in a lymph node, there is no miliary tuberculosis but isolated foci may appear in various organs. At times these foci may be absent and the infection of the organ only be indicated by disease of its corresponding lymph nodes. "In spontaneous infection the bacilli enter the lymphatics only, and the nodes act as a temporary or permanent barrier." In artificial subcutaneous inoculation, on the other hand, the bacilli may enter the blood direct.

From the lymph node infection the reactive processes cause a certain amount of general immunity as indicated by Koch's[13] original experiments. Whereas the first infection may have left no local lesion at the point of infection, it is now quite different and as Smith says: "Clinically, the lymph node tuberculosis of children later becomes an organ tuberculosis, and pulmonary disease becomes the type of later life."

The production of organ tuberculosis would again depend on both numbers and virulence of the invading bacteria.

Tubercle bacilli probably pass through the alveoli of the lungs as soot does, possibly conveyed by phagocytes to the nearest lymph nodes which act

as filters. The bacilli finding a medium on which they can multiply through their ferments being able to split the tissues to suit their needs, the epithelioid cells respond by proliferation to defend the organism. This new tissue undergoes central necrosis and caseation, and the surrounding tissue proliferates and forms a dense capsule, so hedging around the bacilli. From the point of view of the parasite, this process is also a mechanism of defense, according to Smith.

In 1884 Metchnikoff[14] pointed out that in the case of anthrax bacilli inoculated into the blood of lizards, animals which are in general very resistant to anthrax, these bacilli surrounded themselves with a transparent sheath placing themselves in a "state of defense." In a similar manner Metchnikoff found that the tubercle bacillus in the interior of the giant cells of the gerbil and under the noxious substances contained in these cells, envelopes itself in a transparent sheath. The action of the giant cell continuing, a series of such envelopes may be found. Theobald Smith[1, 50] thinks that tubercle bacilli coming from a discharging focus are provided also with some more or less inert protecting substance as an envelope. This envelope has to be removed in some unknown manner both in the body and on culture media before the bacillus will multpily.

The poisoning effect of the tubercle bacillus is twofold. The bodies of the bacteria themselves can cause toxic processes, whilst the metabolism of the bacilli also produces a toxin. Dead bacilli inoculated under the skin can produce abscesses (Koch). The intravenous injections of dead bacilli into guinea-pigs and rabbits cause a wasting away and in time the death of the animals (Prudden and Hodenpyl[15]). The fever production in tuberculosis is however due to the metabolic products of the bacilli, and not to the bacilli themselves (Cornet and Meyer[16]).

Aberrant forms of tuberculosis are most common in childhood. Such are infections of lymph nodes, meninges, bones, joints, etc. Theobald Smith thinks this is because the tubercle bacillus is keyed to adult life and chiefly to the lungs where as a true parasite it can have access and egress.

Tissue Selection.

The tubercle bacillus has been found in practically all the tissues of man, yet infection of muscle tissue and brain substance is indeed rare. Councilman's[17] description of tuberculous brain tumors is worth quoting: "Elsewhere in the body tuberculosis, save in the unusual types of the disease in the lymph nodes, but rarely appears in tumor form. In the cerebral tissue the disease takes the form of distinct circumscribed nodules which may reach the size of a walnut; they are multiple or single, and have little tendency to central softening. They present such differences from tuberculosis elsewhere that before the identity of the disease was established they were given a special designation. They are commonly associated with a chronic form of meningeal tuberculosis which may be the primary or secondary infection. Tuberculosis of the lungs in some degree is always present. The disease is twice as common in the cerebellum as in the brain. The solitary tubercles take the form of hard white masses, round or irregular, and surrounded by a zone of more active

tissue in which miliary points of caseation can be distinguished. The nodule increases in size by the formation of miliary foci immediately around it which becomes included in the central caseous mass."

There can be no doubt that the tubercle bacillus is especially suited to attack the lymph nodes of children and the lung tissue of adults. Should other tissues be invaded, it may be partly the result of accident and partly due to variations in the bacillus or the soil.

The Relation of the Ductless Glands.

The most important recent work in connecting a ductless gland with tuberculosis immunity is that of Lewis and Margot.[18] They observed that in mice and rats infected with virulent cultures of bovine tubercle bacilli an almost constant hyperplasia of the spleen was noticed. Lewis and Margot found that removal of the spleen in albino mice greatly increased their resistance to an intraperitoneal infection and limited the generalization of the infection. That such a result was not due to interference with the distribution of the bacilli through the portal circulation was proved by subsequent experiments. In these it was found that splenectomized mice which had become tolerant to the feeding of splenic tissue showed no more resistance to tuberculous infection than normal mice. Lewis and Margot conclude therefore that when a spleen is removed some bodily function which makes for susceptibility to infection with the tubercle bacillus is also removed.

An enlargement of the thyroid gland is very frequent in early cases of pulmonary tuberculosis, whereas in late stages of the disease this gland would appear to share in the general atrophy. When enlarged, it is usually soft to the touch.

A small number of experiments were undertaken by Dr. Gilbert and myself to study the effect of the removal of the thyroids upon tuberculosis in guinea-pigs. Portions of the thyroid gland varying from three-fourths to the whole amount were removed under ether. Under similar conditions, the thyroids of the control pigs were exposed but not removed. Four weeks later each pig received in the nipple area a subcutaneous inoculation of forty living virulent human tubercle bacilli. The general results may be briefly summarized as follows:

Series A.—Three-quarters of the thyroid tissue was removed.

1. The general condition and appearance when killed was strikingly different. While the control pigs were thin and emaciated and dying, the others were fat and healthy in appearance.
2. The amount of tuberculosis produced did not differ materially in the two sets of pigs.
3. Local lesions were more frequent and prominent in the controls.
4. Hyperemia of the remains of thyroid tissue was noted at autopsy.

Series B and C.—All thyroid tissue was removed.

1. The extent and distribution of the tuberculosis were not affected.
2. The pigs without thyroids showed marked signs of myxedema.

In general, tuberculous guinea-pigs which have been killed during the course of the disease have shown enlargement of the thyroid gland.

The influence on the course of established tuberculosis was also studied. The tuberculous pigs from whom the thyroids were removed died earlier and had more extensive tuberculosis than the controls.

These experiments would seem to suggest that in tuberculous infection in guinea-pigs the thyroid gland tends to hypertrophy but that any decided bearing on immunity processes is not detected.

In chickens infected with the "Spirocheta Gallinarum" enlargement of the spleen and also of the thyroid gland has been noted. Launoy and Bruhl[19] experimented with this disease after the removal of each of these glands and they were unable to determine that their removal increased the resistance of the animals. Removal of the thyroid did not modify the infection. Removal of the spleen appeared to increase the rapidity of the disease.

Clinicians have noted the increase of temperature at the menstrual periods of tuberculous women. The effect of tuberculosis on menstruation can be quite marked, so that upwards of 50 per cent of cases may suffer from some degree of amenorrhea. In advanced cases many tuberculous women cease to menstruate, and this has been noted also in the earlier stages, especially in young girls. We see not uncommonly tuberculous women having hemoptysis at every menstrual period for several consecutive months. Macht[20] in summarizing the influence of menstruation on a tuberculous process states:

1. There can be an aggravation of all symptoms and accentuation of physical signs.
2. The effects of "ovulation" may continue after the menstrual flow has been suppressed.
3. Periodic variations in temperature are very common and occur in probably 50 per cent of all cases.

Hollos[21] believes that such toxic phenomena in tuberculous women stand in some relation to the degree of immunity possessed by the individual.

The Relation of the Blood.

Bartel[22] noted a defensive action of the lymphocytes to tuberculous infection. It has been long recognized that lymphocyte cells take a large share in the formation of tubercles. Bergel,[23] also Marie and Fiessinger[24] were able to prove that lymphocyte cells contained a lipase which could split the wax of tubercle bacilli. Tubercle bacilli themselves have also been found to contain a lipase. Such a quality may help to explain the selection of tubercle bacilli for lymph nodes. It would seem possibly a paradox that lymphoid tissue should exhibit a definite role and yet be the choice selection for these bacilli.

Murphy[25] showed in animals whose lymphoid tissue had been destroyed by x-rays a greater susceptibility to tubercle bacilli.

Children have a larger number of lymphocytes (6,000 per cm.) in their blood than adults, and this increased number diminishes at puberty to the adult picture (3,000 per cm.).

For a long time it has been noted that the blood platelets were usually in-

creased in all forms of tuberculosis. Nature rarely increases such elements without a definite purpose. Leucocytosis in pneumonia and in other affections is better understood since the phagocytosis discoveries of Metchnikoff.[26]

We[27] have reported experiments which would indicate that blood platelets either carry or supply opsonins. Duke[28] has shown that these elements are decreased by large injections into guinea-pigs and rabbits of different bacterial elements but that small doses stimulate an increased production of platelets. We have found in a few cases of miliary tuberculosis a great diminution of platelets, but in almost all cases of pulmonary tuberculosis and in the tuberculosis of laboratory animals we have noted an increase of these elements.

Artificial Immunization against Tuberculosis.*

Almost the greatest prize in preventive medicine today is to find a method of immunizing the human race against tuberculosis. With hygiene alone smallpox cannot be controlled, and it is safe to say that hygiene will never be sufficient alone to prevent tuberculosis. America has always been in the front ranks in endeavoring to discover a method of immunization. I would refer the reader to a review of these efforts in a paper by the author[29] in 1908. The foreign work is reviewed well by Cornet and Meyer.[16]

We must remember at the start, that in successful vaccination of all diseases known today, absorption of the virus by phagocytosis is the essential condition of success. The tubercle bacillus does not lend itself to such absorption.

In any discussion of artificial immunization we must always recall the early experiments of Koch.[13]

"If a normal guinea-pig is inoculated with tubercle bacilli, the point of inoculation very soon closes. After ten to fourteen days there appears at this site a small hard nodule which finally ulcerates. This shows no tendency to heal, and remains so until the death of the animal. If, however, an already tuberculous guinea-pig is similarly inoculated, while the point of inoculation also closes, no indurated nodule appears. Instead, a necrotic process of the skin sets in after the second day, which finally terminates in the casting off of the slough and the formation of a flat ulceration that heals rapidly. Neither do the neighboring lymph nodes become infected. It does not matter whether living or dead tubercle bacilli are used for the second injection."

Romer[30] found that tubercle bacilli injected into a tuberculous animal might not be destroyed at the site of inoculation but could be held in the tissues in a living and virulent state without the production of a tuberculous lesion, and even multiplication might take place. He failed to demonstrate a lytic process such as can be observed in the Pfeifer phenomenon for instance.

Manwaring and Bronfenbrenner[31] claim to have demonstrated a lytic process brought about by the peritoneal cells in tuberculous guinea-pigs. They proved that such power was not connected with any substance present in the circulating blood.

*Since this was written a paper has appeared in the *Journal of Out-door Life* by Dr. Victor G. Heiser, in which it is claimed that tuberculosis has been practically eradicated from the State of Victoria. Further confirmation of this will be needed, yet the methods employed seem well worthy of being copied.

Kraus and Hofer[32] found that tubercle bacilli injected into the peritoneal cavity of tuberculous guinea-pigs were destroyed quickly by lysis.

Hamburger[33] also demonstrated by experiment that all the bacilli of the second inoculation are not always killed. He found that some months after the second inoculation, a tuberculous process may appear and develop like a primary infection.

Romer[30] has shown that Koch's original experiments only hold good provided:

1. The first infection must be a weak one allowing the disease to run a chronic course. (Koch's guinea-pigs had been infected some weeks when he gave the second inoculation.)
2. The intervals between the first and second inoculations must be long enough to have allowed the development of some degree of immunity.
3. The number and virulence of the second inoculation must not be too great.

Vaughan's[34] explanation of the changed reaction to Koch's second inoculation is that the lytic agent which destroys the tubercle bacillus is produced in large amount in tuberculous animals because the cells of these animals have been sensitized and store up a zymogen which is activated when tuberculo-protein is brought in contact with the cell. "The ferment is capable of destroying only a given amount of bacilli or is wholly inactive in the presence of a great amount of substrate, or its action is soon interrupted by the accumulation of fermentative products."

It may be that while some bacilli can be destroyed others have time to develop their protecting sheath and so defy destruction.

In Koch's experiments, it is probable that these bacilli were largely thrown off in the slough, many possibly unchanged.

Koch's conclusions from all his work in the production of immunity to tuberculosis lead him to state that he believed tubercle bacilli could never be absorbed living or dead, and at the same time he would never expect any appreciable immunity to be produced except by the use of living and virulent bacilli.

Calmette[35] is of the opinion that tubercle bacilli are never destroyed by the body cells and is certain they can be eliminated by the bile and at times by the kidneys.

Pathologists agree that they rarely if ever have seen tubercle bacilli undergoing lysis.

Much[36] has claimed that a type of the bacillus free of the waxy covering similar to that sometimes found in early cultures can be discovered in tuberculous lesions and in tuberculous discharges. Much's hypothesis, however, is not yet firmly established and cannot yet be offered in explanation of the disappearance of tubercle bacilli in lytic experiments such as those conducted by Manwaring.[37]

Löwenstein[38] has said that "only the tuberculous organism is tuberculosis immune."

Vaughan has found the tubercle protein to contain less poison than the

cellular protein of the colon and typhoid bacilli. By means of splitting up the cellular substance of tubercle bacilli with alkali in absolute alcohol, Vaughan has obtained a poison similar to bodies which have been procured from bacterial vegetable and animal proteins. Given in sufficient quantities, the poison kills within an hour both healthy and tuberculous animals. Vaughan concludes from his work that no preparation from the tubercle bacilli should be used in the treatment of tuberculosis until the poisonous group of the tuberculous protein be removed.

Obtaining the cellular substance from tubercle bacilli by extracting first with alcohol and then with ether, Vaughan has found that with it guinea-pigs may be sensitized to the tubercle bacillus.

Baldwin[39] and later Krause[40] have made important contributions to our knowledge on sensitization to tubercle protein but have discovered no new procedure so far in the production of appreciable immunity to tuberculosis.

Krause's conclusions are as follows:

1. Sensitization of nontuberculous guinea-pigs with tubercle protein does not alter their resistance to experimental tuberculous infection.

2. Sensitization to tubercle protein and relative immunity (increased resistance) to infection can occur coincidentally in the same animals.

Besredka[41] believes that of all varieties of vaccines, sensitized living vaccine is able to develop the maximum amount of protective substances. To prove that the use of such is without danger in certain diseases, Besredka shows that 15,000 people have been inoculated with a vaccine prepared from living typhoid bacilli without local or general reaction resulting. In addition, hundreds have been treated with living sensitized staphylococci, streptococci, gonococci, etc.

In applying such principles to immunization in tuberculosis, Baldwin[42] has found that by the addition of an immune serum obtained from a cow to living tubercle bacilli, animals became infected more severely than the controls.

We[43] have inoculated guinea-pigs with a minimum lethal dose—about thirty bacilli—after incubation with immune serum obtained from tuberculous guinea-pigs. The resulting infection has been similar to that of the controls.

We[44] have also added to such minimum lethal doses of virulent tubercle bacilli "immune" platelets and "immune" lymphocytes obtained from tuberculous guinea-pigs, and we have found that infection is not constantly avoided and also that the infection resulting has been similar in degree to that of the controls. We do not believe, therefore, that there is any way of sensitizing virulent living tubercle bacilli to render them of service for vaccination.

It would now seem to be quite settled that the inoculation of human bacilli into cattle for immunization purposes has proved a failure, both because of the short duration of the immunity and the dangers from the bacilli getting into the milk.

The partial immunity of animals inoculated with bacilli of low virulence such as in Trudeau's[45] experiments, has possibly always been due to the production of mild unrecognized infections in these animals.

We know today that the human race is constantly exposed to infection by tubercle bacilli, the numbers and virulence of which are matters of chance to

each individual. From such chance infections, however, the race becomes in a crude manner vaccinated to a certain degree against the disease. Nature, however, in doing so, causes the death of many individuals, especially in childhood.

The consensus of opinion among those who have tried to produce immunity in animals is that Koch was correct in recognizing that the living bacillus must be employed. Unlike the successful immunization against typhoid with dead bacilli, in tuberculosis it would appear to be necessary that there should be a struggle between the living bacillus and the living cell before any appreciable immunity is registered. Such a contest is probably one of ferment action.

This was indeed the basis of the original hypothesis of Welch,[46] that "in the struggle between the bacteria and the body cells . . . each participant is stimulated by its opponent in the production of cyto-toxins hostile to each other, and thereby endeavors to make itself immune against its antagonist."

Besredka[41] has shown that in general animals immunized with living sensitized organisms develop some agglutinating power, but their serum has a high bactericidal power and is rich in antibodies. Animals, on the other hand, immunized with heat-killed organisms develop a marked agglutinating power, but their serum is weak in bactericidal powers and the amount of antibodies is negligible.

In tuberculosis, the protection due to antibodies would seem to be of secondary importance to that due to the lytic powers of the fixed tissue cells.

Antibodies such as specific lysins are not easily demonstrated in the blood of tuberculous animals or people.

The parenteral introduction of foreign proteins in general is followed by the production of specific antibodies. Such specific antibodies have not yet been shown to be of the nature of specific protective ferments. The work of Opie[47] and later Manwaring suggest, however, that the tubercle bacillus is opposed by cell ferments.

The lack of very demonstrable specific antibodies in the serum of tuberculous animals would presuppose the failure that has been met in attempts to develop a passive form of immunity. On the other hand, by the use of a special growth of tubercle bacilli as an antigen, Besredka[48] has found that it would seem possible to use the methods of complement fixation to recognize the presence of an active tuberculosis.

With the knowledge we now have that a very few bacilli can produce tuberculosis, it would seem wise to experiment more with definite numbers rather than with moderate quantities of bacilli.

It is realized that practically the whole human race is infected at some time with this disease, and that the infection takes place with bacilli whose numbers and virulence are beyond our control.

The ingenious technic elaborated by Barber[49] for the isolation of single organisms allows us to produce infection of guinea-pigs with a small definite number of tubercle bacilli.

It frequently happens that when a small lethal dose—say twenty virulent tubercle bacilli—is inoculated subcutaneously, no local lesion will be produced.

In such cases, the nearest lymph nodes usually first indicate disease. Similarly the inoculation of a small lethal dose into an already tuberculous pig is never followed by a necrotic process in the skin.

The local lesions of Koch's original experiments hold good only then for the inoculation of quantities or moderate quantities of bacilli, and not for minimal quantities. The processes of immunity, however, indicated by the changed reaction to the second inoculation hold good for all time and are the foundation on which almost all subsequent research has been laid.

Local Immunity.

Smith[1] found that by injecting a suspension of dead tubercle bacilli into the peritoneal cavity of a guinea-pig, in a few weeks the animal became sensitive to tuberculin. Should a second similar dose be injected then into the peritoneal cavity, there is a tuberculin reaction accompanied by fever and loss of weight. This reaction Smith thought to be due to the rousing of a local immunity by his first reaction. Inoculating similar guinea-pigs under the skin, he found there was a slight degree of general immunity, but this was distinctly below the influence imparted locally. Smith advocates the trial of whole bacilli killed by heat at 60° for immunization of the human race, stating that such bacilli are much more efficacious than old tuberculin.

The very objection that Koch found in the bodies of the bacilli forming an abscess Smith feels would be advantageous by causing a local focus as in the subcutis from which immunity might radiate.

Clinical Considerations.

The altered reactivity toward tubercle bacilli in an infected person is spoken of as allergy. This allergy is due to the infecting organism possessing antibodies which can supposedly digest the bacillus and its poisons.

A result, possibly comparable to Koch's second inoculation, is evidenced when an allergic individual is subjected to a new lung infection. A cavity is formed, a result similar to the necrosis and sloughing of the skin as described by Koch, but in this case, healing is not so certain.

A patient with measles is particularly vulnerable to many infections, such as diphtheria, influenza, and especially tuberculosis. Should measles occur in a tuberculous individual, a condition of anergy is produced, and the reaction to tuberculin is lost.

In childhood the condition recognized as scrofula on the other hand brings with it a condition of hyperergy or exaggerated activity. Such scrofulous children usually get well, and later in life would seem to have a higher immunity against pulmonary disease than their fellows.

Baldwin[51] has shown that by the removal of tubercles all sensitiveness to tuberculin disappears, and soon all immunity to the disease is lost. This observer claims that the same thing happens when tubercles become thoroughly fibrous or calcified, and he concludes that in the allergic condition of the tuberculous is contained the relative immunity. It would appear therefore that from

a tuberculous focus a constant stream of some sensitizing material emanates which keeps tuned up the cells of the distant tissues.

When patients are kept under sanatorium regime they regain their tolerance for the bacillus, and the majority of open cases become "carriers." By prolonged rest these people are freed to a very great degree from massive reinfective metastatic doses of the bacilli and are able to withstand small dosage. The regime of sanatorium treatment reduces the allergic condition of the individual, the aim being to promote encapsulation and fibrosis. Clinicians frequently have noted the improvement in health in those cases which have developed a serous pleural effusion. We are observing this possibly more today than formerly, owing to the usage of artificial pneumothorax. From such serous fluids we have readily grown tubercle bacilli.

Baldwin[51] has noticed benefit in such cases when the fluid has been decidedly purulent, and we have also observed similar conditions.

T. von Muralt[52] claims that in pleural exudates there is a decided beneficial effect through absorption of the theoretical antibodies contained in the exudate.

In the human race as age advances, after forty, the death rate from tuberculosis decreases. Elderly people also do not react to tuberculin as do young people, and yet they would appear to have a high degree of resistance to tuberculosis.

Immunization by the Inoculation of Living Organisms Beginning with One or a Few Organisms.

Koch decided that a living and virulent bacillus must be employed to produce successful immunity against tuberculosis. Koch also decided that "we shall not succeed in habituating the organism to absorbing entire bacilli which have been injected subcutaneously; and by injecting small quantities of them, we shall not habituate the organism to absorbing more."

For several years we have been engaged in attempting therefore the seemingly impossible. With a human culture several years old, we were enabled to inoculate guinea-pigs successfully with gradually increased numbers, which totaled many thousand times the lethal dose[54] (M. L. D. 125 bacilli). With recently isolated cultures (M. L. D. 10 bacilli), we have always failed in this method.

Inoculating a series of monkeys[55] (Macacus Rhesus) with gradually increasing numbers of a human culture of which the minimum lethal dose was thirty-five bacilli, we were successful in some monkeys in inoculating totals of over ten thousand times this lethal dose. The examination of the tissues and the injection of different macerated lymph nodes and organs into guinea-pigs failed to show any tuberculosis. We therefore have felt that a true immunity may be produced in this manner.

Unfortunately all monkeys were not so successfully inoculated, and one became infected with even small doses cautiously increased, and before it had reached 1,000 bacilli. Out of a series of six monkeys, four were successfully inoculated and two failed. One of the failures has just been referred to, and in the other case the dosage was increased unusually rapidly. With a culture

somewhat less virulent, we should expect constant success in monkeys, judging by our experiences with guinea-pigs.

The question at once arises, will the modified virulence remain so or will the bacilli after inoculation become more virulent. This question only a larger number of experiments can determine.

Having isolated many cultures from different cases of pulmonary tuberculosis, we have found some variance in their virulence judged by the smallest numbers required to kill guinea-pigs.

The children inoculated five years ago with a culture of which the minimum lethal dose for a guinea-pig was found to be 125 bacilli still remain in perfect health and do not respond to the von Pirquet test. The method is unfortunately not practical and yet further experimentation might make it so.

From our work we have been convinced that infection takes place usually in childhood with very small numbers of bacilli, and that if an immunity in childhood can be raised to even a slight degree we should probably achieve a successful vaccination to tuberculosis.

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TISSUE CELLULAR PROTEIN POISONS*

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VAUGHAN'S protein poison can be derived not only from pathogenic bacteria, but also from nonpathogenic, from proteins of the vegetable world, from albumins or globulins, and finally, as shown in this paper, from the tissue cells of exsanguinated organs of multicellular organisms.

Since as Vaughan has pointed out, although bacteria are usually classified as microscopic plants, yet owing to their chemical constitution they properly belong to the animal kingdom, it was assumed in the work here reported, that the protein poison could be obtained from the tissues from multicellular as well as unicellular animals.

Tissues including muscle, brain, heart, lungs, liver, pancreas, and kidney were obtained from the dog, goat, ox, and rabbit. Because the protein poison can be obtained from blood constituents it was necessary to remove these before clotting occurred, thus securing organs free from water soluble protein. The following procedure was carried out to gain this result with the dog, goat, and rabbit; the animal was first anesthetized, then a glass cannula was introduced into the abdominal aorta; the jugulars were then cut and water was forced under mild pressure into the circulatory system. Several liters of wash water were used in each case, the washing being continued until the fluid running from the jugulars had lost its red tinge. The ox organs were removed immediately after death, and each was washed free from blood by forcing water through its circulatory system. The organs were cut into half-inch cubes and washed in water with frequent changes; the final wash water gave none of the tests for protein. The tissues were then dehydrated in 80 per cent and 100 per cent alcohol each for twenty-four hours. They were then dried and powdered with a fine meat grinder.

Vaughan's standard procedure for splitting off the poison is here quoted:

*From the Hygienic Laboratory of the University of Michigan.

The powdered tissue was extracted in a Soxhlet apparatus, first with alcohol until the wash alcohol was colorless, then with ether for from twelve to eighteen hours. The pure tissue protein thus obtained was dried and then split into its poisonous and nonpoisonous parts with an alcoholic solution of 2 per cent sodium hydrate in the proportion of 250 c.c. of the alcoholic solution to 10 grams of the pure protein. The splitting process was continued for an hour at 78° C., the alcoholic mixture being kept agitated during this time by a mechanical mixer. The insoluble nonpoisonous part was then separated from the soluble poisonous part by filtration. The sodium hydrate was neutralized with hydrochloric acid, and the alcoholic insoluble sodium chloride was filtered off. The alcoholic solution of poison was then evaporated to dryness, taken up again in alcohol to remove the last trace of salt, and finally evaporated. The poisonous residue—the final product—was then powdered.

Tabulation A gives the loss in weight as a result of dehydration and drying, extraction with alcohol and ether, and the final percentage yield of the split poisonous part.

TABULATION A.

SOURCE.	FRESH TISSUE.	DRY SUBSTANCE.	AFTER EXTRACTION WITH ALCOHOL AND ETHER.	PERCENTAGE YIELD OF POISON.
Ox liver	235 gms.	49 gms.	44 gms.	28*
Ox heart	245 "	57 "	37 "	37
Ox kidney	250 "	37 "	33 "	32
**Ox blood cells	2,500 c.c.	2.8 "	2.6 "	25
Dog muscle	320 gms.	82 "	52 "	66
Dog liver	255 "	56 "	43 "	46
Dog spleen	32 "	7 "	5.5 "	36
Dog kidney	52 "	11 "	10 "	31
Dog pancreas	31 "	4.3 "	3.8 "	32

*This is the percentage yield of poison obtained from the protein after extraction with alcohol and ether.

**The ox blood cells were prepared by first drawing the fresh blood into sodium oxalate solution to prevent coagulation. The blood cells were then washed repeatedly with water, their separation being facilitated by centrifugation after each washing. The washing procedure was continued until the cells were free from hemoglobin and serum. So here we have cells which are free from water soluble protein, thus, only that part of the cell remains which enters into the actual makeup of the cell-ground substance.

Tabulation B gives the sources of the poisons, their doses intraperitoneally, and the results in guinea-pigs.

TABULATION B.

SOURCE OF POISON.	INJECTION INTRAPERITONEALLY.	RESULTS IN GUINEA-PIGS.
Ox liver	25 mgs.	Severe symptoms.
	50 "	Peripheral irritation, paralysis, death 12 minutes.
	100 "	Convulsions, death 10 minutes.
Ox heart	25 "	Mild symptoms.
	50 "	Convulsions, death 20 minutes.
	100 "	Peripheral irritation, convulsions, death 23 minutes.
Ox kidney	25 "	Severe symptoms.
	50 "	Per. irr., death 6 minutes.
	100 "	Conv., " " "
Ox blood cells	25 "	Severe symptoms.
	50 "	Per. irr., par. paral., death 17 minutes.
	100 "	Ruf. coat, per. irr., par. paral., death 20 minutes.

TABULATION B.—Continued.

SOURCE OF POISON.	INJECTION INTRAPERITONEALLY.	RESULTS IN GUINEA-PIGS
Dog muscle	25 mgs.	Mild symptoms.
	50 "	Severe symptoms.
	100 "	Par. paral., conv., death 20 minutes.
Dog liver	25 "	Per. irr., par. paral.
	50 "	" " " "
	100 "	Conv., death 12 minutes.
Dog spleen	25 "	Conv., death 20 minutes.
	50 "	Par. paral., lab. resp., death 20 minutes.
	100 "	Conv., death 15 minutes.
Dog kidney	25 "	Mild symptoms.
	50 "	Severe symptoms.
	100 "	Per. irr., par. paral., death 10 minutes.
Dog pancreas	25 "	Quite marked symptoms.
	50 "	Mild symptoms.
	100 "	Per. irr., conv., death 6 minutes.
Dog heart	25 "	Per. irr., ruf. coat, par. paral., conv., death 12 minutes.
	50 "	" " conv., death 18 minutes.
	100 "	Par. paral., death 15 minutes.
Dog lung	25 "	Par. paral., conv.
	50 "	Lab. resp., conv. death 11 minutes.
	100 "	Per. irr., par. paral., death 8 minutes.
Goat muscle	25 "	Ruf. coat, conv., death 20 minutes.
	50 "	Per. irr., conv., death 14 minutes.
	100 "	Par. paral., death 5 minutes.
Goat kidney	25 "	Per. irr.
	50 "	Par, paral., conv., death 17 minutes.
	100 "	Par. paral., ruf. coat, recovery.
Goat spleen	25 "	Par. paral.
	50 "	Lab. resp., par. paral., conv., death 12 minutes.
	100 "	Per. irr., conv., death 8 minutes.
Goat heart	25 "	Per. irr., ruf. coat, par. paral.
	50 "	Par. paral., death 30 minutes.
	100 "	Per. irr., par. paral., conv., death 12 minutes.
Goat brain	20 "	Par. paral., ruf. coat, per. irr.
	30 "	" " " "
	50 "	Ruf. coat, lab. resp., par. paral., conv., death 20 minutes.
Goat lung	25 "	Par. paral., lab. resp., recovery
	50 "	" " " " "
	100 "	" " conv., death 27 minutes.
Goat liver	25 "	Per. irr.
	50 "	" " lab. resp., conv., death 30 minutes.
	100 "	Ruf. coat, " " " " 14 "
Rabbit liver	50 "	Severe symptoms, recovery.
	100 "	Per. irr., conv., death 10 minutes.
Rabbit kidney	50 "	Mild symptoms.
	100 "	Ruf. coat, conv., death 12 minutes.

*Per. irr.—peripheral irritation; ruf. coat—ruffled coat; lab. resp.—labored respiration; par. paral.—partial paralysis; conv.—convulsions.

Tabulation B shows that the toxicity of the tissue cellular protein poison is quite uniform—the average fatal dose, by the intraperitoneal route, being about fifty (50) milligrams.

TABULATION C.

SOURCE OF POISON.	INJECTED INTRAPERITONEALLY.	RESULTS IN RABBITS.
Rabbit liver	380 mgs.	Mild symptoms.
	450 "	Twitchings, lab. resp., conv., death 15 minutes.
Rabbit kidney	450 "	Par. paral., conv., death 30 minutes.
Rabbit heart	350 "	Twitchings, par. paral., lab. resp., recovery.

TABULATION D.

SOURCE OF POISON.	INJECTED INTRAVENOUSLY.	RESULTS IN RABBITS.
Rabbit liver	100 mgs.	Twitchings, per. irr., conv., death 7 minutes.
Rabbit kidney	100 "	" " " " " 12 "
Rabbit heart	100 "	" " " " " 20 "

The results of the experiments reported in Tabulations C and D are interesting from the fact that here it is shown, that the tissue protein poison is toxic for the same species from which it has its origin.

Tabulation E gives the smallest fatal doses of the various protein poisons indicated when these are injected by the intraperitoneal and the intravenous methods in both rabbits and guinea-pigs.

TABULATION E.

SOURCE OF POISON.	INJECTED.	M. L. D. FOR GUINEA-PIG.	M. L. D. FOR RABBIT.
Beef heart	I. V.	0.6 mgs.	90 mgs.
	I. P.	50.0 "	350 "
Goat muscle	I. V.	0.5 "	100 "
	I. P.	50.0 "	380 "
Dog muscle	I. V.	0.75 "	100 "
	I. P.	75.0 "	380 "
Colon poison	I. V.	0.8 "	100 "
	I. P.	75.0 "	500 "
Casein	I. V.	0.6 "	100 "
	I. P.	60.0 "	450 "
Edestin	I. V.	0.6 "	100 "
	I. P.	50.0 "	400 "

The difference in the intraperitoneal and the intravenous dose required to kill a guinea-pig shows (see Tabulation E) that this animal is a hundred times more susceptible to the poison when given intravenously than intraperitoneally; while the rabbit is only four times more susceptible intravenously than intraperitoneally. It would follow then, that one must inject the guinea-pig intraperitoneally with one hundred times, and the rabbit with four times the amount which will actually be absorbed into the circulation.

The guinea-pig and the rabbit are equally susceptible in terms of body

weight when injected with the poison intraperitoneally. It requires about 1 mg. of poison to 4.5 grams of body weight for each species. In contrast it will be noted that by the intravenous route the guinea-pig is killed in the proportion of 1 mg. of poison to 470 grams of body weight; while the rabbit is susceptible to 1 mg. to 18 grams of body weight. It follows then that the guinea-pig is in proportion to body weight about twenty-five times more susceptible intravenously than is the rabbit.

Since the two species, when injected intraperitoneally, are equally susceptible in proportion to their body weights, it follows from the results of the intravenous injections that the guinea-pig takes up poison from the peritoneal cavity less readily than does the rabbit. It must be borne in mind, however, that the guinea-pig is killed by an intravenous injection of one one-hundredth (1/100) of the intraperitoneal dose; whereas the intravenous dose required for the rabbit is as much as one-fourth (¼) of the intraperitoneal dose. So then the guinea-pig is twenty-five times more susceptible, so far as the toxicity of the poison to the circulation is concerned, than is the rabbit, but the rabbit absorbs the poison from the peritoneal cavity twenty-five times more readily than the guinea-pig; consequently when given by the intraperitoneal route the poison is toxic for the two species in proportion to body weight.

From the above consideration of dosage, by the two routes in the two species, the following formula may be applied for the determination of the dosage of an unknown specimen of protein poison; granting, of course, that either dose for either species has been determined by trial.

Assume that the minimum fatal dose of the poison by the intraperitoneal route has been determined, then from the formula,

$$\frac{\text{I. P.* for guinea-pig}}{100} = \text{I. V.* for guinea-pig,}$$

the intravenous dose is determined.

Since the intravenous dose of the poison is in the proportion of 1 mg. to 470 grams of body weight for the guinea-pig, and 1 mg. to 18 grams for the rabbit, the guinea-pig is twenty-five times more susceptible intravenously than is the rabbit; furthermore by the intraperitoneal method of injection both species are equally susceptible in proportion to body weight. Then the formula,

$$\text{I. V. for guinea-pig} \times 25 \frac{\text{Weight of rabbit}}{\text{Weight of guinea-pig}} = \text{I. P. for rabbit,}$$

gives the intraperitoneal dose for the rabbit.

The intraperitoneal dose for the rabbit having been determined, one can now calculate from this the intravenous dose for the same species by the formula,

$$\frac{\text{I. P. for rabbit}}{4} = \text{I. V. for rabbit.}$$

So then, if one determines by trial the minimum fatal dose for either route of injection in either species it is evident that the other three doses can be derived from the above formulæ. In conclusion, then, we find from the formula,

*I. P. means intraperitoneal dose; I. V. means intravenous dose.

I. P. for guinea-pig $\frac{\text{Weight of rabbit}}{\text{Weight of guinea-pig}}$ = I. P. for rabbit, that the guinea-pig and the rabbit are equally susceptible in proportion to their relative body weights. If this is a fact one might reasonably ask: Why is not the rabbit—contrary to experimental findings—as desirable as the guinea-pig for the purpose of demonstrating anaphylactic shock? If minimum fatal doses of specific serum were given intraperitoneally to anaphylactized animals of each species the absorption into the circulation of the guinea-pig of one one-hundredth (1/100) of this dose would kill, and in the rabbit the absorption of one-fourth (¼) of the dose would kill. So then there are injected intraperitoneally into the guinea-pig one hundred (100) intravenous doses, while in the rabbit there are injected intraperitoneally only four (4) intravenous doses. Consequently the chances of variation in the absorption of the poison from the peritoneal cavity of the guinea-pig are far less than they are in the rabbit, accordingly when just the minimum fatal dose is given intraperitoneally the chances of producing anaphylactic shock in the two species are one hundred to four (100-4) in favor of the guinea-pig. Aside from the above consideration which deals with minimum fatal doses it may be pointed out, since the body weights of the two species have not been considered in anaphylactic work, that the chances are about sixteen hundred to one (1600-1) in favor of the guinea-pig. In the experiments presented it is shown that the killing dose intravenously for the guinea-pig is two hundred (200) times smaller than that for the rabbit, furthermore since the anaphylactic injections are usually given intraperitoneally, and the relative weights of the two species are not taken into consideration, it is evident that in such tests the guinea-pig has had from sixteen hundred to two thousand chances to develop shock to the rabbit's one chance. It follows that the conclusion from these experiments coincides with Vaughan's statement "that the guinea-pig is the *par excellence* animal for the production of anaphylactic shock."

The following experiments on rabbits, guinea-pigs, and dogs show the effects of the intraperitoneal, intravenous, and intracardiacal injections of protein poison on the clotting of blood, both *in vivo* and *in vitro*.

EXPERIMENT 1.

Normal rabbit—clotting time of blood 8 minutes.
Goat muscle poison injected intravenously 148 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
2 minutes	2 minutes
Death 3 "	
7 "	5 "

EXPERIMENT 2.

Normal rabbit—clotting time of blood 5 minutes.
Goat muscle poison injected intravenously 50 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
3 minutes	4 minutes
8 "	2 "
20 "	5 "

EXPERIMENT 3.

Normal rabbit—clotting time of blood 9 minutes.
Goat muscle poison injected intravenously 100 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
3 minutes	2 minutes
Death 4 "	
7 "	3 "

EXPERIMENT 4.

Normal rabbit—clotting time of blood 9 minutes.
Goat muscle poison injected intraperitoneally 500 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
3 minutes	3 minutes
8 "	7 "
Death 10 "	
16 "	4 "
21 "	8 "

EXPERIMENT 5.

Normal guinea-pig—clotting time 10 minutes.
Goat muscle poison injected intraperitoneally 100 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
6 minutes	2 minutes
9 "	1 "
Death 10 "	
12 "	4 "
16 "	2 "

EXPERIMENT 6.

Normal dog—clotting time of blood 4 minutes.
Goat muscle poison injected intracardiacally 100 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
3 minutes	3 minutes
6 "	2 "
10 "	4 "
Death 13 "	
13 "	4 "
17 "	4 "

EXPERIMENT 7.

Normal rabbit—clotting time of blood 3 minutes.
Casein poison injected intravenously 50 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
3 minutes	3.5 minutes
8 "	2 "
13 "	1.5 "

EXPERIMENT 8.

Normal rabbit—clotting time of blood 5 minutes.
Morphine sulphate injected subcutaneously 10 mgs. per kilo.
Casein poison injected intravenously 500 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
Death 2 minutes	
3 "	3 minutes
7 "	1 "
10 "	1 "

EXPERIMENT 9.

Normal dog—clotting time of blood 4 minutes.
Morphine sulphate injected subcutaneously 10 mgs. per kilo.
Casein poison injected intravenously 500 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
4 minutes	10 minutes
16 "	7 "
20 "	15 "
23 "	90 "
29 "	90 "
52 "	90 "

EXPERIMENT 10.

Normal dog—clotting time of blood 5 minutes.
Morphine sulphate injected subcutaneously 10 mgs. per kilo.
Casein poison injected intravenously 50 mgs. per kilo.

Clotting time after injection.

Bled from heart after	Clotted in
5 minutes	*
9 "	*
19 "	*
30 "	*
50 "	*

*Not clotted in 24 hours.

Tissue cellular protein poisons, in either large or small doses, hasten the clotting of the blood of the rabbit, guinea-pig, and dog *in vivo*. The protein poison from casein differs from these in that it either retards or prevents entirely the clotting of dog's blood.

Edmunds failed to observe any effect upon the clotting of dog's blood when bacillary protein poison was injected. Underhill and Hendrix report that the injection in large doses of protein poison prepared from casein and zein prevent the clotting of dog's blood, this effect being comparable to typical proteose poisoning. Their results are similar to those of experiments 9 and 10 reported in this paper. It will be noted, however, that the smaller dose of casein poison had the greater power of inhibiting the clotting of dog's blood. Although these results are obtained with casein poison it is shown in experiment 6 that the injection of a small dose of goat muscle poison tends to accelerate the clotting of dog's blood. Here we have opposite effects resulting from the injection into dogs of these two protein poisons, thus showing that conclusions drawn from results of experiments with any single protein poison cannot be applied to protein poisons as a group.

In none of our experiments (1 to 8) *in vivo* on rabbits and guinea-pigs with protein poison have we found that the injection retards the clotting of blood; acceleration of clotting, on the contrary, is noted.

Since the tissue cellular protein poison from goat muscle and also the bacillary protein poison, have no effect on the clotting of dog's blood, whereas casein

poison has a decided retarding effect, the difference in the physiological effect may serve to differentiate casein poison from the other two groups.

The following experiments with protein poisons were carried out for the purpose of determining the effect of these poisons on the clotting of fresh blood *in vitro*.

EXPERIMENT 11.

Normal rabbit blood made up to	Clotted in
.24 per cent goat heart poison	9 minutes
.6 " " " " "	10 "
.9 " " " " "	19 " Jelly clot
1.8 " " " " "	30 " " "
3.05 " " " " "	180 " " "
4.15 " " " " "	*
4.99 " " " " "	*
5.6 " " " " "	*
6.4 " " " " "	*
7.0 " " " " "	*
8.0 " " " " "	*
9.0 " " " " "	*
Control	3 "

*Not clotted in 24 hours.

In experiment 11 the percentage (0.9 per cent) of goat heart poison necessary to inhibit clotting—if we accept the terminology of Underhill and Hendrix, "that the blood was considered clotted when the containing cylinder could be inverted without the loss of a drop"—*in vitro* was about the same as that of casein poison used on dogs *in vivo* by Underhill and Hendrix, and in which there was no coagulation of blood. It will, however, be noted in the following experiment (Experiment 12) that rabbit's blood must be made up to 1.8 per cent casein poison in order to prevent clotting. Inasmuch as in both experiments (11 and 12) blood of the same species was employed, it would again appear that the different physiological effects of these two poisons are shown in the clotting of blood.

EXPERIMENT 12.

Normal rabbit blood made up to	Clotted in
.0005 per cent casein poison	3 minutes
.005 " " " "	3 "
.01 " " " "	3 "
.05 " " " "	3 "
.12 " " " "	5 "
.18 " " " "	4 "
.56 " " " "	6 "
.61 " " " "	5 "
.84 " " " "	4 "
1.12 " " " "	7 "
1.4 " " " "	7 "
1.6 " " " "	8 "
1.8 " " " "	*
3.5 " " " "	*
Control	3 "

*Not clotted in 24 hours.

EXPERIMENT 13.

Normal rabbit blood made up to	Clotted in
.24 per cent Witte's peptone	2 minutes
1.0 " " " "	2 "
2.0 " " " "	2 "
2.5 " " " "	2 "
3.0 " " " "	3 "
3.5 " " " "	2 "
4.0 " " " "	3 "
4.5 " " " "	3 "
5.0 " " " "	3 "
7.5 " " " "	3 "
10.0 " " " "	4 "
Control	3.5 "

In contrast to the effect of the protein poison on the clotting of rabbit's blood *in vitro* it is shown in experiment 13 that Witte's peptone produces the opposite effect.

EXPERIMENT 14.

Normal dog blood made up to the following percentages of casein poison.	Clotted in 9 minutes	Normal dog blood made up to the following percentages of ox liver poison.	Clotted in 10 minutes
.24.		.24	
.5	8 "	.5	9 "
.75	9 "	.75	9 "
.9	19 "	.9	23 "
1.6	20 "	1.6	25 "
2.0	95 "	2.0	95 "
3.0	*	3.0	*
3.5	*	3.5	*
4.0	5 "	4.0	4 "
Control	7 "	Control	7 "

*Not clotted in 24 hours.

Experiment 14 shows that from 0.24 to 0.75 per cent of ox liver poison and the same percentage of casein poison have but little effect on the clotting of dog's blood; there is a well-defined retardation for from 0.9 to 2.9 per cent; the inhibition is complete for 3.9 to 3.5 per cent; while there is acceleration of clotting with the 4.0 per cent solutions of these poisons. It will be noted that the percentages of these two poisons run parallel to each other as to their influence on the clotting of dog's blood *in vitro;* it will be observed, also, that *in vitro* a much larger percentage of casein is required to prevent the clotting of dog's blood than *in vivo*. If we assume that the ox liver poison has the same effect on the clotting of dog's blood as goat muscle poison *in vivo* (Exp. 6), may we not conclude, since the percentage employed *in vivo* is nearly represented by the .24 per cent *in vitro*, that probably the tissue cellular poisons have similar effects on the clotting of dog's blood both *in vivo* and *in vitro*.

Conclusions.

1. Vaughan's protein poison can be prepared from tissue cells of the exsanguinated organs of multicellular animals.

2. The tissue cell protein poisons are not only toxic for heterologous species, but also for homologous species.

3. The M. L. D. of the protein poisons—here reported—for the guinea-pig and the rabbit is in proportion to their relative body weights when given by the intraperitoneal method of injection; when given intravenously, however, it is, in proportion to body weight, twenty-five (25) times more toxic for the guinea-pig than the rabbit.

4. Tissue cellular protein poison hastens the clotting of blood from the guinea-pig, rabbit, and dog *in vivo*. The protein poison prepared from casein differs from these in that it either retards or prevents entirely the clotting of dog's blood.

5. Witte's peptone does not prevent the clotting of rabbit's blood *in vitro*.

6. The *in vitro* experiments here reported show that all the protein poisons tested inhibit the clotting of blood from the guinea-pig, rabbit, and dog, in certain percentages.

LABORATORY METHODS

An Automatic Pipette*

By Albert H. Rowe, M.S., M.D., San Francisco, Calif.

THIS pipette has been in use for several months while estimating albumin and globulin in blood sera by Robertson's[1] method. The instrument has proved so satisfactory that it is described in this paper with the hope that it will be found of help in other laboratories where repeated measurements of small amounts of fluids must be made.

For the operation of the pipette a constant supply of compressed air and suction (produced by an ordinary suction pump) is necessary. The photograph shows the arrangement of the apparatus in the size most convenient for use in Robertson's method.

The pipette (a) can be of any style or size. If 1 or 2 c.c. of liquid are to be measured, Folin's modification of Ostwald's pipette is most convenient. If it is desired to measure larger amounts either the ordinary volumetric or Mohr's pipettes may be employed. For Robertson's technic, the pipette is best made of small tubing 2.5 mm. in bore and 30 c.c. in length. The small size of this tube helps accurate measurement and allows the pipette to be inserted into the tubes of 5 mm. bore, thus facilitating their filling. As only equal amounts of different fluids of approximately .5 c.c. volumes are used, it is only necessary to make one mark with a file on the pipette near the .5 c.c. level.

The pipette is held in place by being fitted snugly into a rubber stopper (b) which is inserted into a hole in the cross beam of the frame. To the upper end of the pipette a glass bulb (c) is attached to prevent fluid being suddenly sucked into the pump. To this bulb, a "T" tube (d) is joined, the left arm of which is connected by means of a three way stopcock with the compressed air and the right arm by means of a similar stopcock with the suction pump. These stopcocks (e) are fastened securely to the uprights of the frame. The handles of these stopcocks pass through the center of cardboard dials which bear inscriptions denoting the action of the suction or air when the handles are turned in the indicated directions. Attention is called to the fact that at point (f) on the left dial, a nail is inserted which prevents the handle being turned into a position where there is no escape for the compressed air, which occlusion would blow out the tube connections. If the compressed air contains moisture it is well to run it through a large empty bottle before it comes to the instrument.

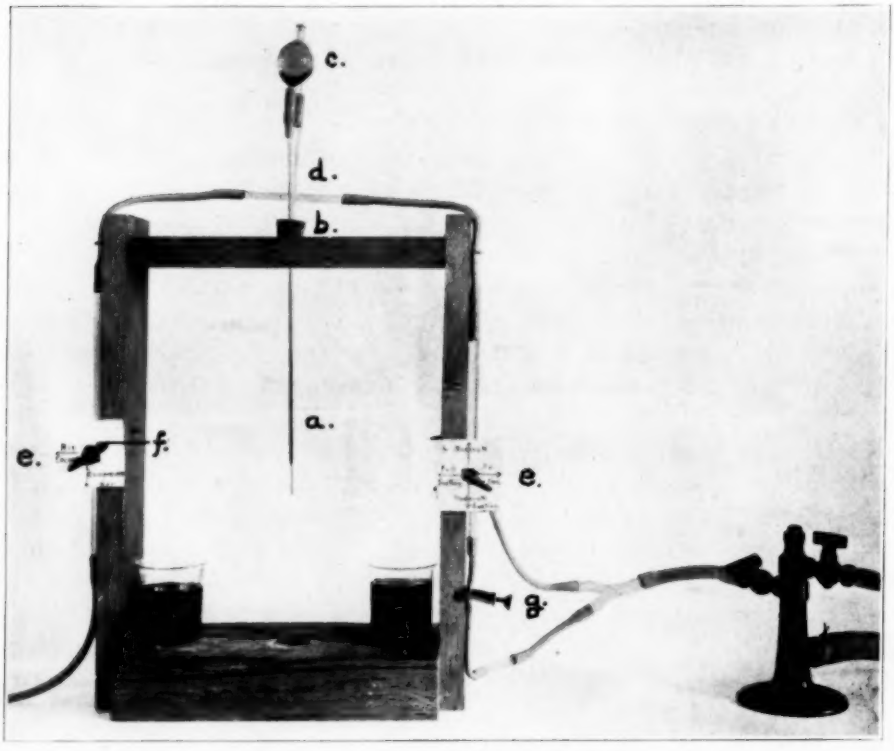
The stopcock on the right has one of its arms filed off so that the remain-

*From the Chemical Laboratory and the Medical Service of the Massachusetts General Hospital, Boston.

[1]Robertson, T. B.: Jour. Biol. Chem., xxii, p. 233, 1915.

ing one indicates, by reference to the dial, the action that suction exerts on the pipette. When the handle of the stopcock is turned to the left full suction is exerted on the pipette. In the vertical position, the suction varies according to the degree of closure of the rubber tube by the Hofmann's pinch-cock (g), fastened distal to the dial on the upright of the frame. This pinch-cock can be so regulated that fluid is drawn up into the pipette very slowly. When the handle of this stopcock is turned to the right, suction is cut off and fluid in the pipette is held stationary. It is best to draw the fluid up a little beyond the desired mark and suck it down to the correct level by a piece of filter paper held to the opening of the capillary end.

If compressed air is used to discharge measured fluid from the pipette, it



is done rapidly. But when atmospheric pressure is allowed to enter the upper portion of the pipette by loosening or pulling out the left hand stopcock, the fluid will run out slowly by gravity. The latter method of emptying is often required in Robertson's technic, especially where serum is added to an equal amount of saturated ammonium sulphate solution, by use of which method the serum is introduced so gently that it overlies the sulphate solution and does not mix with it until the tube is shaken.

In Robertson's method, it is frequently necessary, in order not to waste fluid, to clean and dry the pipette before each measurement. This is done by drawing water, alcohol, ether and finally air up and down the pipette. By turning both air and suction into the pipette but having the force of air consider-

ably greater than that of the suction, it is possible to draw the fluid up and down very quickly by merely turning the air on and off.

It is necessary to add that the pipette must be absolutely clean so that no fluid will remain on the inner surface of the tube after it is emptied of its contents. Therefore, it is well to draw cleaning fluid into the pipette, leaving it there when the pipette is not in use. It is even better to have several pipettes so that one can be used which has been in cleaning fluid for several days.

The Schick Test*

By Don M. Griswold, M.D., M.P.H., Detroit, Mich.

THE development of the Schick test is one of the recent advances in modern medicine. It is unique in that it does not enter the field of diagnosis or treatment, but is concerned entirely with the immunity or susceptibility to disease.

The diagnosticians and therapeutists have had their day, and now the immunologists appear to have a real contribution for science.

The so-called skin tests date from von Pirquet's work on tuberculosis. The intradermal test for that disease has traveled as far as propaganda of the fight against the Great White Plague. Skin tests have been developed later for gonorrhoea, syphilis, typhoid and diphtheria. The information sought is the presence or absence of disease in all these tests, except the diphtheria test. In this test the determination of susceptibility or immunity of the patient to diphtheria is the object sought.

Physiological chemistry is a wonderful field, and extensive as our knowledge might seem we have only scratched the surface. To put HCl and $NaHCO_3$ in a test tube and explain the evolution of gas is comparatively simple. The reason it is simple is because the chemical characteristics of both these substances are very well known. To the person not possessed of this chemical data, the evolution of gas would seem quite wonderful.

And should it not seem equally as wonderful to any of us that we can take certain chemical substances called amboceptor, complement, etc., of which we know nothing regarding the chemical composition, and determine whether our patient has syphilis or not. In dealing with reagents, of which we do not know the chemical character, our test tube results must always be interpreted in the light of our scant knowledge. As one of my former teachers so often said: "Please to remember, gentlemen, a human stomach is not a test tube."

So it seems fitting that such men as von Pirquet, Park, Kolmer and von Schick, should spend many months or years upon tests which leave out of consideration the inanimate test tube, and utilize the human body as a place for physiologico-chemical reactions to be studied. Of course the skin is the part

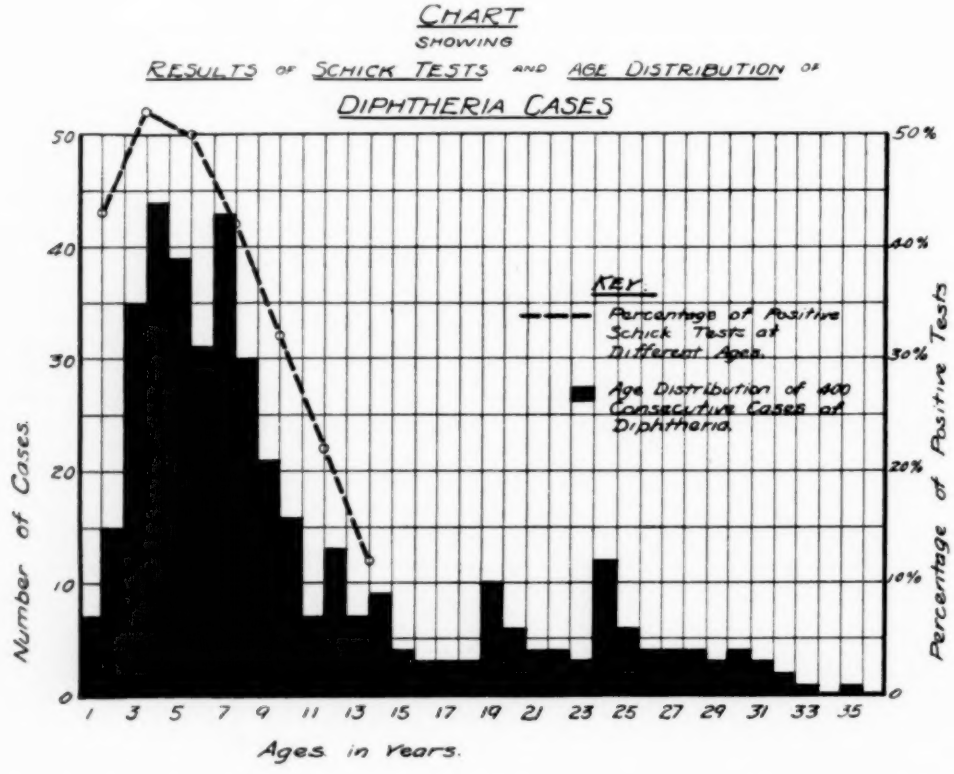
*From the Laboratory of the Detroit Board of Health.

of the body most easily accessible. Inflammation of the skin gives least annoyance to the patient, and is a point most easily determined.

Von Pirquet built the foundation for this line of research when he announced that by applying old tuberculin to abrasions of the skin, characteristic inflammation occurred in tuberculous individuals.

Von Schick, working with the acute contagious diseases in the same clinic, attempted to use the same fundamental principles for work on diphtheria.

Römer has shown that persons who take diphtheria uniformly have less than 1/30 unit of diphtheria antitoxin per cubic centimeter of their blood serum. He also found that persons who were exposed to diphtheria over long periods of time, such as nurses, internes and doctors, who never took diphtheria, uni-



formly showed more antitoxin in their blood serum than would be expressed by 1/30 antitoxic unit. From this he concluded that immunity or susceptibility to diphtheria depended upon whether the individual possessed more or less than 1/30 of an antitoxic unit in each cubic centimeter of his blood serum.

This is a piece of purely scientific data. Von Schick realized how valuable this piece of information would be if the test for 1/30 of an antitoxic unit per cubic centimeter could be made rapidly and simply enough to allow it to be used in routine work. He found that if 1/50 of an M. L. D. of diphtheria toxin be diluted to 1/10 of a cubic centimeter, and the same injected intracutaneously, that persons susceptible to diphtheria would show a red area about the site of the in-

jection, and that immune persons would show no such reaction. The basis of this reaction is, of course, the irritating properties of diphtheria toxin. This irritating toxin injected into the skin of an immune person is immediately neutralized by the antitoxin in the circulating blood, and no reaction is to be seen. When the test is applied to a susceptible person, there being no free circulating antitoxin (or at least less than 1/30 per cubic centimeter), the toxin lays there between the layers of the skin, and in twenty-four to forty-eight hours a slight redness is seen about the site of the injection.

The technic is so simple that it can be acquired by a few trials and can be done very rapidly. In running a large series of these tests, it soon becomes evident that only 30 to 35 per cent of the people are susceptible to diphtheria, and that the remaining 65 to 70 per cent are naturally immune and could not take the disease. This gives the words "naturally immune" a new meaning, because now we know that it is definite diphtheria antitoxin which brings about this immunity and not pleasing generalities of the past "robust constitution," "perfect physical condition," etc.

The percentage of positive Schick tests agrees very closely with the incident of diphtheria for the different ages as is shown by the chart. If we take as proven, that two-thirds of all persons are naturally immune to diphtheria, the question arises at once of the advisability of giving antitoxin promiscuously to all exposures to diphtheria. It stands to reason that two-thirds of the antitoxin will be given to individuals who already have enough to protect them.

The rational procedure would seem to be to give antitoxin to all clinical cases, and a Schick test to all exposures; the following day to read the results of the test and immunize all susceptible persons. The length of time that passive immunity is given by injections of antitoxin has been discussed at length. The only available data being the occurrence of diphtheria in persons immunized by antitoxin.

The Schick test gives us data along this line:

I have found six people who would take a Schick test every second day after they had recovered from diphtheria. The earliest recurrence of a positive Schick was three weeks after 20,000 units of antitoxin. The longest time that 20,000 units gave immunity was six weeks.

To Summarize.—The Schick test seems to give us a quick, easy way of determining whether a person is susceptible to diphtheria. Its use will eliminate needless giving of antitoxin to persons exposed to this disease. It will lessen the danger of anaphylaxis in a community because there will be fewer sensitized persons. It is the greatest single step forward in immunology and serum therapy since the advent of diphtheria antitoxin itself.

Simple Test for Estimating Chlorides in the Urine, Founded on Volhard's Method

By J. J. Seelman, M.D., Milwaukee, Wis.

THE following test for estimating chlorides in the urine is accurate to within one-half gram per liter, and can be made in from three to five minutes. Two solutions are made up as follows:

SOLUTION NO. 1.

Anhydrous, crystallized silver nitrate, (C. P.)	29.055	gms.
25% nitric acid in distilled water	900.	c.c.
Cold saturated solution of ammonioferric alum in distilled water	50.	"
Distilled water, q. s.	1000.	"

SOLUTION NO. 2.

Ammonium sulphocyanate	7	gms.
Distilled water	1000.	c.c.

The test can be performed with ordinary 1 c.c. pipettes graduated to .01, separate pipettes being used for the urine and for each solution to prevent contamination. I find nipple pipettes more convenient, and have had three pipettes made which I use for this test only. One is a .5 c.c. pipette, one a 1 c.c., and one a 2 c.c. graduated to .05.

Solution No. 2 is purposely made too strong, and must be standardized by adding distilled water in such an amount that exactly the last drop of 2 c.c. of this solution will bring about the end reaction when added to 1 c.c. of Solution No. 1. The end reaction consists of a reddish-brown color, which does not disappear on moderate stirring. If the second last drop produces a discoloration which disappears rather slowly, and the last drop a deep brown color, the solution must be still further diluted, until the discoloration on the addition of the last drop is a light reddish-brown, which does not disappear on stirring fifteen to twenty seconds.

The test proper is performed as follows: Place .5 c.c. of the urine to be tested in a small porcelain dish. Add 1 c.c. of Solution No. 1 and stir about one minute with a glass rod. From a pipette graduated to at least .05 c.c. add Solution No. 2 drop by drop, stirring after each drop until the brown color which develops disappears. When the brown fails to disappear after about fifteen seconds' stirring the end reaction has been reached. Read off the exact amount of Solution No. 2 which has been used to bring about the end reaction. The difference between this and 2 is equal to the number of grams of sodium chloride per 100 c.c. of urine. Example: 1.15 c.c. brought about the end reaction. 2.00—1.15=.85 gms. per 100 c.c. or 8.5 gms. per liter of urine. If 20 gms. or more per liter are present, as evidenced by the end reaction being obtained with the first drop, the urine is diluted with equal parts of distilled water, which is, of course, allowed for in the subsequent calculation.

It is advisable to maintain three pipettes for this work, using them for no other purpose. They can be marked X, 1 and 2. The first is used for the urine only, the second for Solution No. 1, and the third for Solution No. 2. This prevents contamination of solutions, which would throw them out of adjustment. If desired, pipette No. 2 can be marked to give direct reading of sodium chloride in grams per liter.

A no inconsiderable advantage of this method is the fact that only very small quantities of the reagents are required for each test.

A Rapid and Accurate Clinical Method for the Estimation of Sugar in Small Quantities of Blood

By J. J. R. Macleod, M.B., Cleveland, Ohio.

THE attention which has been given to the elaboration of methods for the determination of sugar in small quantities of blood, has been due to the fact that no one method has really been satisfactory. The method may have been accurate enough (e. g., those of Rona and Michaelis, or of Frank), but required too large a quantity of blood to make it practicable in clinical practice, or it may have met the requirements in this regard but have been too complicated and uncertain for use by any others than those who had originally worked it out, or had at least devoted much time and care to learning it (e. g., the so-called micro method of Bang).

It is therefore most important that a simple method which is not only accurate but can be applied to small amounts of blood (1-2 c.c.) should at last be available. The originators of this method are Lewis and Benedict, but it has since been simplified by R. G. Pearce and by Myers and Fine.

Like all other methods for the estimation of sugar, this new one depends on the reducing power of a protein-free filtrate of blood. Instead of using copper salts to indicate the extent of the reduction, however, the conversion of picric into picramic acid is chosen. Since the latter forms a deep red solution, the extent of reduction can be ascertained by using a colorimeter.

The Lewis-Benedict method as modified by R. G. Pearce is carried out as follows: 2 c.c. blood, immediately after withdrawal, is mixed with 8 c.c. of water in a test tube and allowed to become thoroughly laked; 15 c.c. of a saturated watery solution of picric acid is then added, the test tube well shaken and the resulting precipitate of protein removed by filtration. Of the filtrate, 6 c.c. are placed in another test tube and mixed with 2 c.c. more of the picric acid solution and 1 c.c. 10 per cent sodium carbonate solution. Usually two such aliquot portions of the filtrate can be secured, thus permitting of duplicate analysis. The tubes are then placed in an autoclave at a pressure of 2.5 kg. per sq. cm. (or about 20 pounds to the square inch) for 15-30 minutes. After being allowed to cool, the contents of the tubes, now more or less red in color, are

poured into 10 c.c. measuring flasks and the volume in each case made up to 10 c.c. with distilled water. Comparison of the depth of color is now made in a colorimeter (Duboscq) with a standard consisting of either (1) a picramic acid solution of such a strength that the color corresponds to that produced by 0.48 mg. of dextrose under the above conditions (i. e., 0.048 gm. picramic acid and 0.100 gm. anhydrous sodium carbonate dissolved in 1000 c.c. water), or (2) a blank estimation made exactly as above described with a known amount of dextrose (preferably 0.48 mg. in 10 c.c.). By using standards of the above strength the readings on the scale of the instrument are directly proportional to the sugar concentration; e. g., suppose the standard is placed at 10, this must correspond to blood containing 0.1 per cent dextrose (because 6/25 2 c.c. or 0.48 c.c. of blood were used), so that if the unknown read 8,* the percentage must be $10/8 \times .1 = 0.125$, and if it read 12 the percentage is $10/12 \times .1 = .083$, and so on.

In Myers' and Fine's modification, the use of the autoclave is dispensed with and simple heating for 15 minutes in boiling water is substituted. To make this possible, however, a lower dilution of the blood is necessary.

The method is carried out as follows:

Two c.c. of blood are discharged into a small test tube containing 8 c.c. of water. After laking, 0.2 gm. of dry picric acid is added and dissolved by stirring with a glass rod. After the protein is completely precipitated, the tube is allowed to stand for several minutes with occasional stirring. It is then centrifuged and the supernatant fluid filtered into a dry test tube through a small thick dry 5-7 cm. filter paper. Three c.c. of the filtrate is placed in a tall graduated test tube, and after adding 1 c.c. of 20 per cent sodium carbonate solution, the tube is placed in a boiling water bath for 15 minutes. After cooling, the volume is made up with distilled water to 10, 15 or 20 c.c., depending on the depth of the color. This is then compared either in a Duboscq or a Hellige colorimeter with a standard. If the Hellige colorimeter is available the wedge is filled with a solution prepared by dissolving 0.100 gm. of picramic acid and 0.2 gm. of anhydrous sodium carbonate in a liter of water. The calculation in this case is carried out by subtracting the colorimetric reading obtained from 100 and multiplying by 0.002 if the dilution was to 10 c.c., or by .003 if to 3 c.c., and so on. We have not personally tested the accuracy of this modification.

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*The scale reads from below up, zero corresponding to such a position of the plunger that none of the colored fluid is being looked through. The lower the reading on the scale, therefore, the stronger the color of the fluid.

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EDITORIALS

The Pharmacological Action of Chlorine Gas

A LONG series of well-known investigators have in the past devoted themselves to the study of the peculiar and striking pharmacological actions of chlorine gas. Conspicuous among these earlier workers are Böhm,[1] Binz,[2] Lehmann,[3] Jurisch,[4] Herxheimer,[5] etc.

In the year 1887 Lehmann carried out a long series of animal experiments with chlorine at the Hygienic Institute in Munich. He was chiefly interested in the action of the gas from an industrial standpoint, since in the various manufacturing processes workmen were exposed to fumes of the gas. This work was continued by Lehmann and his pupils for a long period, and a whole series of papers on the general subject of poisonous gases were published by these workers. The method used in general consisted in allowing the animal to breathe for longer or shorter periods of time, air containing various definite percentages of chlorine, etc. The immediate and later (or postmortem) symptoms were carefully studied and described. Lehmann confirmed the earlier work of Böhm and others who had observed that the poisonous action of chlorine is chiefly a local one on the respiratory organs. It was found that a concentration of 1 part in 100,000 parts of air produced an irritation of the eyes, nasal mucosa, mouth, trachea and lungs. This concentration, however, was not sufficient to produce death. It was believed by Binz that small quantities of chlorine like these regularly produced a cerebral

depression, but as the concentration of the gas was increased then the irritative symptoms served to completely overcome and mask the previously observed cerebral action. Later writers appear to have dropped this earlier view of Binz. Lehmann also determined that a concentration of 1 part of chlorine in 10,000 parts of air was capable of producing fatal results in a comparatively short time. If the animal did not die immediately, a short exposure was sufficient to produce lesions from which death would probably result many hours later. It is interesting to note also that Lehmann considered the possibility of sterilizing the lungs and respiratory passages by administering chlorine in sufficient concentration to kill the bacteria. This, however, he quickly gave up.

In 1895 Herxheimer called attention to a new feature of chlorine poisoning. This consisted in the production of a peculiar form of acne. This was characterized by multiple abnormalities of the sebaceous glands. Many of these showed no inflammatory symptoms, but were merely scattered about over the skin as white projecting comedones, some filled, others showing a dark-colored discharge. Other glands were inflamed and contained purulent material. These formed small ulcers and led to deep scar formation which might give the affected area a sieve-like appearance. A number of the glands were enlarged into thick-walled atheromatous cysts, some of which showed no inflammatory changes while others were inflamed and contained more or less purulent material. Furunculosis was often observed. As general symptoms were noted headache, sleeplessness, anorexia, emaciation, anemia, vertigo, etc., briefly, symptoms which apparently depended on the anemia. In later years a good deal of discussion has been carried on regarding the real cause of these lesions. It appears that workmen engaged in the electrolytic production of chlorine are the chief sufferers, and it is still undecided whether the condition is produced by free chlorine or by some other unknown body.

Recently a number of investigators have again taken up the question of chlorine poisoning. In the laboratory, Schäfer[6] and Hill[7] especially have done valuable work, while a great many clinical observers have written on the subject.

The symptoms produced by breathing air containing chlorine (1 to 10,000) consist of irritation of the eyes, nose, larynx, and deeper respiratory passages; bronchitis, pulmonary congestion and edema, pulmonary hemorrhages, coughing and pain in the thorax. The amount of irritation produced in the eyes, nose, throat, etc., does not always correspond with the severity of the symptoms which may follow later from the effects of the gas on the lungs, etc. Clinically, there are repeated allusions to the fact that some men appear to stand the action of the gas better than others who have presumably received an equal exposure.

From its chemical nature it seems evident that the immediate action of chlorine must be local. For it is scarcely possible to imagine that it can exist in the free state in such a fluid as blood, which contains many bodies with which it would immediately combine, and which would—unless it were introduced in immense quantities—at once render it inocuous. For chlorine at once displaces hydrogen from its combinations in the proteins and forms hydrochloric acid with the hydrogen set free. And further, it combines with the hydrogen of water

thus liberating nascent oxygen, which then acts on the tissues. These processes are believed to account for the fact that chlorine is a much more powerful disinfectant in moist air than in dry. In the higher organisms all of these reactions probably occur together.

Schäfer saturated Ringer's solution with chlorine gas and then injected the solution intravenously. If only a small quantity were thus introduced no effect was seen, and if a larger quantity, spread over a certain interval of time so that the fluid became well mixed with the blood, were injected, the only result was to produce a quite temporary diminution of blood pressure (preceded by a slight rise) and a slight increase in the depth of the respirations. The fall, Schäfer believed, was due to obstruction of the pulmonary vessels. The diminution in volume of the kidney, which occurred as the blood pressure fell he believed to be passive. These results were produced by the introduction into the jugular vein of a rabbit of 10 c.c. of Ringer's solution saturated with chlorine, the injection being spread over twenty seconds. With inhalation the result is always serious. Even with air containing only 1 per cent of chlorine—although at this dilution no special effect upon either the blood pressure or respiration may be visible for some minutes—a profound change ultimately occurs, and this may show itself with great suddenness. In this case the respirations, while remaining regular both in rate and depth for a few minutes, may suddenly become very deep and in another minute convulsive, prior to complete arrest; while the blood pressure usually falls rapidly and profoundly as the respiration becomes irregular and stops. With 5 per cent of chlorine in the air breathed a fatal result was rapidly and inevitably produced. In none of these latter cases was it possible to revive the animal by artificial respiration. Schäfer considers these effects due to something happening locally in the lungs, since the chlorine which is inhaled cannot be carried to the tissues in a free state. There is moreover, abundant evidence that the tissues retain their vitality even after inhalation of the strongest mixture; for when the body is opened immediately after death, the muscles contract briskly on excitation either directly or through their nerves, and the heart is also responsive to stimulation, and is, indeed, usually seen—especially the auricles—beating spontaneously if somewhat weakly. The only visible change is in the lungs, which even after the shortest exposure to a fatal dose, are intensely red and congested, either all over or in innumerable patches. They are less shrunken than usual, and have a more solid feel, with but little crepitation; nevertheless, even small pieces float in water. On section, the lung is deep red in color, and the tissue seems to be full of blood. There is usually some froth in the trachea and larger bronchi. It is to be noted that if an animal be subjected to a large but nonfatal dose of the gas, and then allowed to live for some time after, other changes than those here described will occur.

The effects which might be produced locally in the lung by an irritant gas-like chlorine are various. It may directly affect the bronchial musculature or the vascular musculature; it may stimulate the mucus-secreting mechanism of the air tubes; it may influence the coagulability or viscosity of the blood within the pulmonary vessels; or it may produce reflex effects by exciting the endings of afferent nerves within the lungs. Schäfer is of the opinion, however, that

the fatal result is due to obstruction in the pulmonary vessels rendering it impossible for the blood to pass freely to the left auricle and ventricle. This latter conclusion he demonstrated by perfusing the lungs in situ in a freshly killed animal. A cannula was tied into the pulmonary artery and the outflow of the solution was collected from the left auricle by means of a second cannula tied into the auricle. The lungs were regularly inflated by an artificial respiration machine. The action of the chlorine was determined by adding Ringer's solution containing chlorine to the solution which was being perfused through the lungs. It was found that even small quantities (1 c.c. of 1 in 10 chlorine Ringer) produced a profound effect upon the pulmonary circulation, the flow through which became greatly slowed almost to complete cessation. Similar results were produced when the chlorine was introduced into the lungs in the air used for the artificial respiration.

In another series of experiments the action of the gas on the bronchioles was studied. Three different methods were used in these experiments (none of these methods seem reliable to the present writer), the final conclusion being that chlorine causes the bronchial tubes to become more permeable (dilate).

Microscopically, sections of the lung showed the pulmonary capillaries gorged with blood, and with an extraordinary amount of edema in the interstitial tissue. Often the edema fluid passed freely into the alveoli, many of which were full of coagulated lymph, some containing blood. Presumably the edema was secondary to the vascular obstruction, but even if this were so it would set up a vicious circle by increasing the obstruction, and this again would increase the edema. That the secretion of mucus did not play an important part in connection with the fatal ending was evident from the fact that death resulted just as inevitably and rapidly after a prior dose of atropine as without it. The liver and abdominal organs possessed a normal appearance postmortem.

Clinically, a good many variations from the above description have been recorded because the patients have generally been subjected to the influence of the gas some hours or days before most of the clinical descriptions were made. During this period secondary changes are set up and complicate the original condition. It is remarked by Hill that the action of the gas on the very extensive surface of the lungs (90 sq. metres) is comparable to the effects produced by extensive burns of the skin, and the same general treatment to support strength and lessen shock is required. Just as septic infection of the skin is the sequel of a burn, so pneumonia and bronchitis follow chlorine poisoning.

The clinical course[8] of cases of chlorine poisoning has been described as passing through three more or less definite stages:

1. The asphyxial stage.
2. The quiescent or intermediate stage.
3. The bronchitic stage.

The first stage begins as soon as the gas is breathed in sufficient concentration. A sense of suffocation and choking together with greater or less irritation of the eyes, nasal mucosa and respiratory passages lead to strong gasping convulsive efforts at respiration. If the patient is removed from the fumes after several minutes, and if a fatal dose has not been received, the symptoms

will progress, being marked by cyanosis, the escape of a light yellowish frothy discharge from the mouth and nose, collapse, and a variable but usually intense degree of asphyxia. Consciousness is not destroyed unless by asyphxia or impending death. The temperature becomes subnormal, there is restlessness, the pulse is slow and full (except in collapsed cases), the expression is strained and anxious. The patient may sit propped up with his head thrown back gasping for breath, or he may lie with his head hanging over the side of the bed attempting to aid expectoration. The respirations are jerky and hurried and often accompanied by a choking cough. With each inspiration the chest is expanded to its fullest and emphysematous areas are often thus produced in the lung tissues. Auscultation shows the presence of moist sounds of different qualities all over the chest.

After some thirty-six hours the first stage usually passes off and the patient may fall into a sleep from which he awakes feeling much better. This stage may last for perhaps half a day. But after these few hours of comparative quiet symptoms of bronchitis may begin to manifest themselves. Fortunately it appears that this bronchitis stage is not always so severe as would be expected. But death may occur from the effects of the poison and its sequelæ at almost any stage of the intoxication. If the bronchitic stage becomes severe the frothing secretion gives way to a thick greenish mucopurulent expectoration, consciousness may be replaced by delirium, the fever rises, the pulse becomes small and rapid, and the respirations increase in number but become shallow and feeble.

The treatment of these patients presents problems of peculiar and uncommon difficulty. It is obvious at once that the patient needs two things, first a full oxygenation of his blood and second, the removal of the carbon dioxide from his blood. Under ordinary conditions these two processes go on together simultaneously by means of the respiration. But in these cases the ordinary methods of aiding nature in carrying out these processes are greatly handicapped on account of the peculiar condition of the lungs and respiratory passages. For the patient may be continually struggling about and trying to expectorate so that any method of artificial respiration so far tried is used only at a considerable disadvantage. Large quantities of a frothy yellowish fluid clog the air passages and are expectorated with difficulty. Postmortem this fluid is seen to completely fill the small air passages while the finer ones are entirely lost in a condition of intense congestion and edema which affects the lungs as a whole, the congestion involving the mucosa of the entire respiratory tract. The first object of treatment has been to try to get rid of some of this exudation which is drowning the victim. Emetics have proved useful in a large number of cases. Half a pint of salt and water or 8 grains of copper sulphate, followed by large drafts of lukewarm water, have been recommended. Vomiting may be promptly initiated by brushing the back of the throat with a feather or the patient's finger. The act of vomiting has been reported to cause the expulsion of a large quantity of the frothy fluid. As emetics vinum ipecacuanhæ and apomorphine hydrochloride do not appear to have been so satisfactory as salt and water. Atropine, amylnitrite, stramonium, chloroform inhalations, etc., do not appear to have been

of any substantial benefit, as indeed might be expected from theoretical considerations. Ammonium carbonate (10 grains every 3 hours) as a "stimulating expectorant" seems to have been of some real benefit. Vinum ipecacuanhæ given along with this has also been said to be of value. Opium may be of value in cases that suffer a good deal from local irritation, etc. The patient should be kept warm and otherwise made as comfortable as possible, and plenty of fresh air should be available. Muscular movements, vigorous treatment, etc., should be avoided when possible on account of the increased demand on the patient's limited supply of oxygen in the blood.

Lastly, and perhaps in the severer cases most important of all, we come to the administration of oxygen. Hill has studied this question very carefully. Various methods and forms of apparatus have been used, but none so far seem to be entirely satisfactory. The cost of oxygen when used by ordinary clinical methods such as administering it through an open funnel held near the mouth and nose, is very great and the benefit is very small. Hill found that when oxygen was administered to himself by an attendant in a London hospital, the oxygen in his own alveolar air was increased by only 1 or 2 per cent. If, however, a loose kind of face-mask were made out of a towel, and the oxygen tube were led under that, and the oxygen were sent in in a sufficient stream to blow away the exhaled carbon dioxide, then 70 per cent of oxygen could easily be obtained in the alveolar air. But a 20 ft. cylinder of oxygen is soon exhausted by these methods. To give oxygen economically and continuously, some closed method must be used. A device by which this may be done has recently been described[9] in this journal. Hill further found that compressed air was of distinct benefit to animals in this condition. The whole animal was placed in a compressed air chamber in which a pressure of two atmospheres was produced. This not only increased the amount of oxygen (dissolved) which passed into the animal's blood, but it also reduced by one-half the size of the air-bubbles in the frothy liquid which obstructed the air-tubes, thus relieving the obstruction. Artificial respiration, e. g., by the method of Schäfer sometimes has been of distinct help clinically, especially in carrying the patient through a brief crisis. It must not be forgotten that the patient's blood is also loaded with carbon dioxide, and other acids also, such as lactic, are increased in quantity owing to the lack of oxygen. In many instances it has been found that the administration of oxygen for brief periods at a time at intervals afforded distinct and prolonged relief to the patient.

Other diverse forms of treatment,[10] such as bleeding, cupping, leeching, injection of large doses of camphorated and etherized oil, the hypodermic administration of strychnine, sparteine, oxygen, pituitary extract, brandy, adrenaline, sodium cacodylate, etc., inhalations of steam impregnated with compound tincture of benzoin or with eucalyptol, the application of mustard plasters, administration of "ethone," the application of large linseed meal poultices, etc., have been tried. From a theoretical standpoint it is often difficult to understand how a patient who had been severely poisoned by breathing chlorine could live through some of the courses of treatment described. Strangely enough the clinical reports from most forms of treatment are fairly favorable, except for the desperate

cases, the majority of which apparently usually die in the early stage of the poisoning.

It is only to be expected that numerous complications may arise from chlorine poisoning. Some of these have been briefly referred to in recent literature. Bronchitis and pneumonia are the immediate sequelæ of the poisoning. Nephritis as a later development has been frequently mentioned. Fibrosis of the lungs and angina pectoris are also suggested. Pojarisky[11] has reported changes in the blood, especially in Bizzozzero's blood plates, and in the walls of the vessels. the endothelium. He believed that from these changes the blood is increased in coagulability. This "thickening" and increased coagulability of the blood is repeatedly mentioned in cases where bleeding was attempted and carried out only with difficulty. Postmortem Pojarisky frequently found miliary hemorrhages in the brain. After the third day he observed such complications as putrid bronchitis, partial pulmonic gangrene, pleurisy, embolism, hemorrhagic infarcts, etc. These may lead to permanent disability even if there is recovery from the immediate effects of the gas.

As a prophylaxis against chlorine poisoning various forms of respirators have been devised. The literature on this phase of the subject, however, appears to be very meager at present. Bollay long ago recommended the use of a large sponge soaked in anilin solution (poison!) which was to be supported before the nose and mouth in order to absorb the gas. Obviously the eyes should be protected from the effects of all concentrated vapors of chlorine. This can be done by a mask with glass windows. Apparently if protection is required against only dilute vapor, then a mask made of several layers (Jurisch suggests 30) of moist flannel may be sufficient. If, however, concentrated vapor is met with, the mask should be moistened with a solution of some chemical capable of neutralizing the chlorine or of arresting its passage into the mouth and lungs. Sodium thiosulphate has been recommended for this purpose, the reaction taking place as follows: $Na_2S_2O_3 + 4\ Cl_2 + 5\ H_2O = 2\ NaCl + 2\ H_2SO_4 + 6\ HCl$. The sodium thiosulphate is used in dilute solution and a little sodium hydrate may be added.

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—*D. E. J.*

The Uric Acid of the Blood

MUCH has been written in the past on the uric acid of the blood, and in no other field, probably, have the reported findings been of so little value. Not only in the medical profession, but also, secondarily, of course, and excusably, among laymen, there has been much loose talk regarding an "increase of uric acid in the blood."

It is only a little more than three years that accurate knowledge as to the uric acid content of the blood has been available. For example, Saleeker,[1] in 1909, reported the finding of 5 parts of uric acid in 1,000 parts of blood in a gouty subject, and, as uric acid was not demonstrable by quantitative methods in health, this finding was looked upon as evidence that there is an increased concentration of uric acid in the blood in gout. Brugsch and Schittenhelm[2] have gone so far as to say that uric acid is lacking in normal blood, while its presence points to the existence of gout.

Folin and Denis,[3] in 1912, published their method for the quantitative determination of uric acid in small amounts of blood, and were able to show that this substance is a normal constituent of blood, being present in quantities of 1.5 to 2.5 mg. per 100 c.c. of blood. At the same time they were able to show that in gout, lead poisoning, leukemia and some cases of nephritis, the uric acid may be considerably increased.

More recently, Folin and Denis[4] have published a comprehensive paper on the diagnostic value of uric acid determinations in the blood. The large accumulations of urate deposits in the joints and cartilages in gout indicate strongly the probability of an augmented amount of uric acid in the blood. But, as a result of several hundred quantitative determinations of uric acid in the blood in different conditions, the authors feel convinced that uric acid determinations alone are not of great value in the differential diagnosis of gout and other arthritides.

Their studies have shown, too, that the uric acid values of blood bear no fixed relation to the values for nonprotein nitrogen. Four possibilities present themselves, as they point out:

"1. Blood in which both uric acid and nonprotein nitrogen are present in normal amounts.

"2. Blood in which, with normal amounts of uric acid, we have greatly increased amounts of nonprotein nitrogen.

"3. Blood giving abnormally high uric acid values with normal amounts of nonprotein nitrogen.

"4. Blood in which abnormally large amounts of both uric acid and nonprotein nitrogen are present."

They then append tables illustrative of each of the four groups. In group I are normal individuals as well as patients suffering from alcoholic gastritis,

[1]Saleeker: Deutsch. Arch. f. klin. Med., 1909, xcv, p. 353.
[2]Cited by Folin and Denis.[3]
[3]Folin, O., and Denis, W.: Jour. Biol. Chem., 1912, xi, p. 527.
[4]Folin, O., and Denis, W.: Arch. Int. Med., 1915, xvi, p. 33.

cystinuria, diabetes insipidus, arteriosclerosis and cardio-renal disease (one case each), insanity (four cases), and chronic interstitial nephritis (two cases).

In group II, with normal uric acid and high nonprotein nitrogen (50 to 110 mg. per 100 c.c.), are found cases of acute arthritis (three), chronic arthritis (five), nephritis with prostatectomy (one), bone tuberculosis (one), and mitral stenosis (one).

Of great interest is group III, consisting of twelve cases, with high uric acid (3.3 to 5.4 mg. per 100 c.c.) and normal nonprotein nitrogen. Eight of these patients had typical gout. In two patients gout was probable but there were no tophi. Of the two remaining cases, one was a "normal man, many members of whose family have been gouty" and the other a patient who "has passed several vesical calculi consisting of pure uric acid."

The final group IV, with increase in both uric acid (3.3 to 10 mg. per 100 c.c.) and nonprotein nitrogen (59 to 326 mg. per 100 c.c.), is based on observations on fourteen cases. There were four cases of uremia, three of arthritis deformans, one with "weak heart,, edema of the lungs, hypertrophic arthritis," one of pneumonia, one with cardio-renal disease, two with nephritis, one with acute gonorrheal arthritis, and one case of "acute gout, tophi, chronic interstitial nephritis."

To quote further from Folin and Denis, "Gout is characterized by abnormally high uric acid content of the blood without any abnormally high accumulation of other waste products (nonprotein nitrogen). Exceptions may, of course, occur; gouty patients may also have nephritis. Nephritis in the gouty is usually of the arteriosclerotic type, a type which, according to our experience, is not accompanied by an excessive accumulation of nonprotein nitrogen in the blood (except in the terminal stages). This rule is, however, unfortunately not without exceptions."

Thus, it is evident that quantitative determination of the uric acid of the blood alone is of little service in the differential diagnosis of gout and other arthritides. To make it of value, a determination of the nonprotein nitrogen of the blood must be made at the same time. If the uric acid alone is increased, the finding speaks strongly for gout. If both uric acid and nonprotein nitrogen are above normal, the blood findings are more suggestive of arthritis of other origin, though the possibility of gout plus nephritis must be borne in mind.

The estimations which Folin and Denis report have been made with their method. The patients have been on a purin-free diet for at least two days before the blood for analysis was drawn.

More recently, Denis[5] has reported experiments on the effect of diet on the uric acid content of the blood.

Observations have been made on patients after a period of purin-free diet and, again, after a purin-rich diet. The blood was always drawn before breakfast, to avoid the possible effects of a recent meal. It has been found that in normal men "no increase in the circulating uric acid is produced by the ingestion of large quantities of purines. In persons suffering with renal insuffi-

[5]Denis, W.: Jour. Biol. Chem., 1915, xxiii, 147.

ciency, a more or less marked increase in the uric acid content of the blood is produced by high purine feeding." Indeed, this accumulation of uric acid may be found there before there is any rise in the nonprotein nitrogen. Denis concludes that "when the determination of uric acid in the blood is undertaken as a diagnostic test, the insistence on a preliminary period during which no purine-containing foods are consumed is unnecessary, except in cases in which kidney insufficiency exists, or perhaps in the case of persons who habitually consume extremely large quantities of purine-containing foods."

—*R. S. M.*

The Pituitary in Hibernation

THE dominant manifestations of hibernation are lethargy, storage of fat, decreased tissue combustion, associated with lowering of the body temperature, bradycardia, slowing of the respiration, lowered blood pressure, and insensitivity to painful or emotional stimuli.

Cushing, Crowe and Homans[1] noticed in their cases of experimental hypophysectomy that after the operation the dogs became lethargic and finally died in coma. They noticed that associated with these symptoms there was a noticeable lowering of the body temperature together with slowed respiration, bradycardia, low blood pressure and insensitiveness to external stimuli. They likewise noticed that when not enough gland was removed to produce the fatal cachexia hypophyseopriva that the animals tended to accumulate fat and to lose their sexual activity, and to be drowsy and apathetic with slow pulses and subnormal temperatures, a total symptom picture which simulates that known in human beings as dystrophia adiposogenitalis. These symptoms were relieved by the use of pituitary extracts. So, from the experimental as well as from the clinical sides there was evidence of a distinct similarity between pituitary insufficiency and hibernation.

Recently Cushing and Goetsch[2] have studied the ductless glands of hibernating woodchucks with the result that they have found very noticeable changes especially in the pituitary glands. They found that the glands were decreased in size and that the cells of the pars anterior had lost their characteristic staining reaction to acid and basic dyes. Also they found that at the end of hibernation the glands enlarge and the cells regain their normal microchemical reactions, and also increase in number.

In this work is given very interesting proof of the fact that what is a normal physiological process in an animal is abnormal in the human even though the appearances are identical. The difference may be that in the one the process is temporary; in the other permanent. It makes one stop and wonder whether it is quite safe to base so many experimental conclusions on the similarities in the morphological or even the chemical reactions in human and animal tissues without knowing the specific physiological relationships.

[1]Cushing, Crowe, and Homans: Bull. Johns Hopkins Hosp., 1910 (21) 127.
[2]Cushing and Goetsch: Jour. Exper. Med., 1915 (22) 25.

—*P. G. W.*